Journal

OF THE UNIVERSITY OF TORONTO

MEDICAL SOCIETY

FEBRUARY 1964 VOLUME XLI NUMBER 4

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Medical Horizons: "A Minority of One"

Seven days aboard ship after leaving Genoa, Italy — seven sunburnt Mediterranean days broken by brief jaunts into Naples and Athens — we arrived at our destination of Haifa. My purpose: to work as an extern in a hospital near Tel Aviv.

The hospital, like all things Israeli, I found to be new. It lay surrounded by lush green lawns, flowering shrubs and trees, and enhanced by a large pool marking its entrance. Quite remarkable when less than ten years ago there was nothing here but yellow sand! This was Beilinson Hospital, comparable in size to the Toronto Western Hospital, and only one of many large hospitals in a country with only two million inhabitants.

Even more remarkable than the great number of hospitals, as I learned later, was the plentiful supply of Doctors. In spite of having only one small medical school in Jerusalem, Israel has more Doctors per capita than any other country in the world. As disclosed by recent statistics gathered in 1958, Israel has 420 inhabitants per physician as compared to 920 in Canada. This is a result of the massive immigration since the last World War that has brought Doctors from many distant places: from European centres in Britain, Austria, Germany, Poland and Hungary, from Turkey and even South Africa — each bringing his own discipline. Together, a high standard of medicine has resulted with all fields of specialty represented by eminent men, together with the most modern facilities. This is in marked contrast to ten years ago when antibiotics could only be obtained in emergency situations — and not always then. This was definitely a good setting for a conscientious and keen student of medicine to learn.

Alas, I did not speak Hebrew. But regardless, the Doctors were most willing to explain problems to me in English — one of the many languages they all seemed to speak. However, after several weeks of plying about the wards, a friend and I decided to devote our time to being tourists rather than doctors, influenced, of course, by the staff who thought we were crazy to spend our summer in a hospital. "Live here; they encouraged, but spend your time seeing Israel". And so we did.

From Eilot on the Red Sea, where the borders of Israel are squeezed to a few miles width by Egypt and Saudi Arabia, we travelled north up through the barren Negev desert, a wasteland that comprises most of Israel. Silently, under the cover of night, the Black-tented Bedouin Arabs still steal across Jordanian-Israeli borders — their's being a home that knows no boundaries. Also, this is the haunt of the Fellaheen's, terrorists from Egypt, who will sometimes shoot up a lonely car that should have waited until daylight before going north.

Hence, we went to the Dead Sea, the lowest place on earth, to swim and to roam about archeological treasures at nearby Massada — the mountain-fortress of Herod against the Romans — still untouched by commercial tourism. Farther North to Nazareth, the Christian centre of Israel, to the Jordan, and to the Sea of Galilee we went doggedly attempting to assuage our guilt feelings of neglected bloods and retractors.

But Israel is a land of social contrasts as well as scenic. Fifty percent of the population have their origin in near Eastern culture and the rest are of Western European culture. It is said that a girl from Yemen and a man from Europe makes a fine marriage, but the reversed relationships will only end in chaos.

Spiritualistic values are contrasted in Israel to a great extent. For example: Tel Aviv, regarded as the playground of Israel with its pulsating nightlife of cafes and cabarets, it's secular materialism, and whose inhabitants are atheistic to the point of never observing any religious holidays, is contrasted with Jerusalem, the religious centre of Israel where a small fanatical segment of the population regard Israel only as a State of God.

Apart from Israel's varying landscape, our brief visits to the hospital also left fond memories: the weekly meal of fishheads complete with eyeballs, the singsongs on the grass in the cool starlit evenings (Israeli nurses were even up on the latest American twist hits via their local version of CKEY), the Out Patient Breast Clinic on Tuesday mornings when we seemed to examine literally hundreds of cystic mostitis, and finally when our interest was revived, — but that's another story.

And then, after one and a half months, we left Israel, feeling the summer, now only half over, to have been a memorable one.

D. Chubb 6T4

Editorial

This edition of the journal is devoted to areas of medical neglect. Canadian medicine is insular, and understandably so, for until global meridians were squeezed together by jet bindings a decade or so ago, tropical diseases remained in the tropics and we in Canada complacently retained our good old temperate phyla of illnesses. The continuity of this pattern is being disrupted. Those medics concerned with large volumes of "Canadian" patients are becoming increasingly aware of the broadening spectrum of disease and are concerned with their inability to diagnose early, and treat effectively such "bizarre" diseases as leprosy, chronic malaria and the gamut of parisitic infestations which they are encountering in ever increasing numbers. Disease patterns, which in their endemic areas, would be spotted at a glance, have become the nemeses of diagnosticians here and have often gone undiagnosed until they are either far advanced or until the pathologist utters his views in conclusive and mocking tones.

The first paper deals with this problem of a contracting world and the resultant expanding field of diagnostics. The author speaks from his own experience at the Toronto General Hospital Outpatient Department and as a medical student.

With the increasing *awareness* of parasitic disease, comes the inevitably apparent secondary increase in its incidence and the paradox of better diagnosis breeding disease is manifest. It would be an understatement to say that most new graduates from this centre are ill-prepared for dealing with parasitic disease, knowing little more than a cursory description of a few complicated life cycles which inevitably involve feces. Diagnosis and treatment escape them entirely.

Our second paper which also stems from the O.P.D. of the Toronto General deals with important parasites encountered in Ontario. The author, a fourth year medical student, has very competently surveyed the outpatient records, and has found several facts which will be of interest and likely of use to us all.

To add further to what you may already consider "canaries", I have chosen two articles which must certainly fall into this category:— *Cytomegalic Inclusion Disease* and *Toxoplasmosis*. The truth of the matter lies in the papers — which I hope you will read — but suffice it to say that these are much more common that is generally supposed. To most of us they are just rare birds memorized in the course of a long differential diagnosis, and placed purposely at the end of the list as a reflection of their acclaimed rarity. I trust that the discussions here will serve to elevate these much maligned, down-trodden, bottom-of-the-list "canaries", if not in 'list position', at least in your own personal estimations!

It has been the conviction of members of the Journal staff that the fruits of valuable A.O.A. papers should not fall unreaped. For the past years, crops of excellent discussions have gone fallow in the closed sanctuary of A.O.A. meetings. In this edition an abridgment of a collective paper on transplantation is added with a view to clarifying the broader aspects of a field which one day may have one of us sporting a baboon's kidney or an artificial heart. In this area the disparity between fact and fiction is rapidly being bridged.

The purpose of this edition is to breed an awareness, and to face a problem before the problem faces us. Laugh as you like now but let us also have the last guffaw.

H.T.

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On the Importance of Geographical Information in Taking a Medical History

Richard M. Gladstone

International travel is commonplace today. As a result, the urban physician can expect to see more and more of the type of disease that 50 years ago was confined largely to other parts of the world. With this in mind, I believe that an addition should be made to the standard method of history-taking known to all medical students. In addition to a discussion of the social, educational, occupational etc. histories of your patients, it would often be very rewarding to spend a few moments discussing a Travel and Geographical History as well. If the patient is an immigrant or a foreign visitor to this country, you should enquire about endemic and epidemic diseases in *his* country, and about the liklihood of his having parasitic, worm or fungal infestations. In certain cases, the country of origin of the patient may be enough to give you a good clue as to what to expect and suspect when you interview the person. A native of Ethiopia may complain to you of crampy abdominal pain and diarrhoea; in this case you would be wise to suspect Taenia saginata (beef tapeworm) because of the high degree of infestation in that country. Similarly, an otherwise unexplained febrile illness and chest infection may become clearer after finding out the patient had been touring the Western United States and spent some time in the San Joaquin Valley. The student should also be familiar with the various "goitrous" areas of the world in which endemic goiter is common. It is believed that the incidence of hyporthyroidism and carcinoma of the thyroid is higher in these areas. In Great Britain, the areas especially known are Hook Norton in Oxfordshire, South Wales and parts of Derbyshire. In the U.S.A., the Great Lakes Basin is a well known goitrous area. In India, the entire northern part of the subcontinent is an area of intense endemicity. In Mexico, goiter is common and there is also a high prevalence of deaf-mutism and mental deficiency. Goiter is exceedingly common in Yugoslavia, especially in Bosnia, an area in which syphilis is also endemic. In parts of Australia and New Guinea, goiter is frequently found.

An increasing awareness that common symptoms may have uncommon causes, and be specifically related to the country of origin of the patient, with its different climate, food, fauna, flora; different vectors of disease, methods of sanitation etc., is becoming more and more evident. Recently, I saw as a patient, a student that was suffering from bronchial asthma and chronic bronchitis. The fact that he was from India and was studying here as a Commonwealth scholar did not seem to make any difference to my diagnosis at the time. It was not until I did a differential blood count and found an eosinophilia of 65% that I turned to the textbooks and discovered that what this man really had was Tropical Eosinophilia, in which bronchial asthma, occuring in spasmodic attacks, is only part of the syndrome. Now, whenever I see a patient from India, Ceylon, China, or Africa who complains of cough, paroxysmal dyspnea with wheezing attacks I will include Tropical Eosinophilia in the differential diagnosis. This realization happens to be quite important because this disease has its own specific treatment and is not greatly benefited by the usual anti-asthma remedies.

If a patient comes to you complaining of chronic cough and hemoptysis, a certain group of diseases and specific methods of investigation come readily to mind. But, if this patient is Chinese and has recently immigrated to Canada, his presenting symptoms take on new meaning, after you have taken a Travel and Geographical History. It may then turn out that he does not have a bronchial adenoma, nor lung cancer, but he is actually suffering from a disease called Paragonimiasis (endemic hemoptysis). This is something you probably never would have suspected until you asked him about his travels within and outside his homeland, the diseases that are common there, and the dietary habits of the people. It was only then that he told you he had once gone to visit his relatives in Manchuria where they feasted on the local delicacy — crab meat. Perhaps then you would have vaguely remembered something about crabs acting as a host for the lung flukes. After a bit of page-turning, you would read in your bacteriology notes, after first dusting them off, that Paragonimus westermani invades the lungs of human beings and animals, giving rise to fibrosis of the lungs and chronic hemoptysis. This is associated with chronic cough and copious sputum which is watery, mucoid, or muco-purulent. It is often streaked with bright red blood and orange flecks which consist of masses of eggs. In this case the patient almost made the diagnosis himself, after the proper leading questions.

Another cause of chronic cough and hemoptysis in a native of China, especially if from the Yangtze

River Valley, Shanghai or Canton is a disease called Bronchospirochetosis. This illness is characterized by fever and attacks of violent coughing, during which large quantities of frothy, sticky, often blood-streaked sputum are brought up. This chronic, hemmorrhagic bronchitis is due to an infection with Spirocheta bronchialis and is often referred to as Castellani's bronchitis.

Hematuria is another presenting complaint that is often puzzling. Would YOUR investigation be any different if the patient concerned was an Egyptian rather than a Canadian? Most certainly it would, for you would be wise to suspect Schistosomiasis (Bilharziasis), a disease that has been widespread in Egypt since antiquity. In fact, it is so common that Egyptian peasants regard blood in the urine as a sign of puberty, and may not tell you of any urinary abnormality on functional enquiry. However, this disease should remain in the back of your mind whenever you are examining anyone from Egypt or Africa who has a genito-urinary complaint, especially those which turn out to be hydronephrosis, urethral stricture, cystitis etc. for they may well be due to urinary Schistosomiasis.

In China and Japan, this disease takes a different form. The causative agent is Schistosoma japonicum, and the illness begins with an initial dermatitis, prolonged fever, urticaria and eosinophilia, the so-called Katayama syndrome. Later it progresses to splenomegaly, hepatomegaly and in 50% of cases, cirrhosis of the liver. The following table should be of value when assessing liver enlargement, particularly in patients from Tropical countries.

Some cause of Liver Enlargement:

I *Liver Enlarged and often Tender*	II *Moderate and Gross enlargement*
Amebic hepatitis	Kala-Azar
Amebic liver abscess	Trypanosomiasis
Infective Hepatitis	Schistosomiasis
Pyogenic liver abscess	Clonorchiasis
Malaria	Opisthorciasis
Relapsing Fever	Fascioliasis
Undulant Fever	Hydatid Disease
Leptospirosis	Actinomycosis
Schistosomiasis	Histoplasmosis (progressive)
	Sickle Cell Anemia
	Thalassemia

I *Liver enlarged and often Tender*	II *Moderate or Gross Enlargement*
Visceral larva migrans	Cirrhosis following:
Ascariasis	Hepatitis
Congestion in cardiac failure:	Parasitism
Myocarditis	Malnutrition
Beri-Beri	Alcoholism
Epidemic Dropsy	Storage Disorders
Endocarditis	Storage Disorders:
Endomyocardial fibrosis	Fatty infiltration (Kwashiorkor)
Hepato-veno-occlusive disease	Amyloidosis
Sickle Cell Anemia	Hemochromatosis
Thalassemia	Carcinoma-primary or secondary
Chagas Disease (South American)	Syphilis
	Leukaemia
	Lymphadenoma
	Chronic Heart Failure
	Constrictive Pericarditis
	Hepatic veno-occlusive disease

Epilepsy is another interesting problem when it occurs in someone who has lived in Africa, Egypt, India, China or the Mediterranean Area. In rare cases, the epileptic fits may be due to such diseases as Echinococcosus, Schistosomiasis, or Cysticercosis.

An enlarged spleen in a person who is otherwise healthy may indicate a previous attack of malaria. This disease is still very common in India and Ceylon, Africa, Greece, Italy and Turkey. The Canadian physician may never see a patient with the initial rigors and fever of malaria, but may see him many years later as a diagnostic problem with pyrexia of unknown origin. The patient may be afebrile and symptomless for many months after the initial illness and then explosive episodes may occur. This is especially true of Subtertian or Malignant malaria, the most dangerous form of the disease. In this form the rigors are less marked but very severe anemia can occur rapidly. Involvement of internal organs can simulate many other diseases, because of the intense toxemia produced when the growing forms of Plasmodium falciparum agglutinate and sporulate in the capillaries. This causes blockage and local damage from released toxin and pigment, with consequent impairment of the circulation. Pernicious attacks with hyperpyrexia, delirium, coma, mania, convulsions, paralysis, and memory disturbances can occur and resemble very closely such well known clinical entities as uremic or diabetic coma, pontine hemorrhage, or cerebro-spinal meningitis.

When a patient from any of the malaria-prone countries presents with splenomegaly plus additional symptoms, it is wise to realize that Subtertian Malaria may also take the following forms:

Gastric — with vomiting, epigastric pain, and occasionally hematemesis

Choleraic — with profuse diarrhea and collapse, resembling Cholera.

Dysenteric — with blood and mucus in the stools, resembling Bacillary dysentery.

Purpuric — this form presents with intradermal haemorrhages

Oedematous — this form shows general anasarca, resembling wet Beri-Beri.

Syncopal — with acute heart failure, resembling cardiac disease

Anemic — with acute and severe hemolytic crises

Nephritic — with red blood cells and casts in the urine, resembling nephritis

Gangrenous — with gangrene of the extremities

Appendicular — with pain in the right iliac fossa, resembling appendicitis

Cholecystic — with pain over the gall-bladder

Icteric — with deep jaundice

Virulent — this is the estivo-autumnal form which is transmitted by the unclean syringes of heroin addicts in New York, Cairo, and Peking.

Many years after an initial bout a patient may present with "malarial cachexia." This is a chronic condition, following one or more malarial attacks, with a persistent secondary anemia, sallow or even icteric skin, edema and emaciation, often an enlarged liver and always splenomegaly. There is usually an irregular, recurring fever. Functional disorders are common, and this condition may be the cause of recurrent abortion in pregnant females, and of retardation of growth in children.

The common clinical evidences of malaria that one should keep in mind are: (1) splenomegaly (2) periodicity of fever and symptoms (3) persisting urobilinuria (4) history of possible exposure to infection or residence in a malaria area (5) fever (6) characteristic blood cell counts, types of blood cells etc. (7) microscopic demonstration of the parasites. There is likely to be a leucopenia and a definite increase in mononuclears, which if up to or above 15% is practically diagnostic.

The following table should be of interest when assessing splenomegaly.

Some Cause of Splenomegaly:

I *Spleen enlarged and often Tender*

Malaria

Typhoid Fever

Typhus Fever

Undulant Fever

Relapsing Fever

Rat-bite Fever

Trypanosomiasis

Glandular Fever

Septicaemia

Bacterial endocarditis

Tuberculosis

Infective hepatitis

Blackwater Fever

Sickle Cell Anemia

Thalassemia

Iron-deficiency Anemia

Erythraemia

Acholuric jaundice

Splenic infarct

II *Moderate or gross enlargement*

Malaria

Kala-Azar

Undulant Fever

Portal Hypertension:
- Hepatic cirrhosis
- Schistosomiasis
- Banti's syndrome
- Portal or splenic vein thrombosis

Myeloid Leukaemia

Lymphatic Leukaemia

Lymphadenoma

Myelfibrosis (rare)

Amyloidosis

Lipid Storage diseases (rare)

Who ever thought that they would see a case of Leprosy in Toronto? Certainly not the nodular or lepromatous form anyway. While rare in this country, Leprosy still affects millions in India, China, Africa and the islands of the South Pacific. In the Outpatient department of the Toronto General Hospital I saw a case of neuro-anaesthetic leprosy in a young student from India. He believed that he had ringworm, and said that many of the people in his home town had a similar affliction. This type of neuro-anaesthesia is common in the tuberculoid form of leprosy. In this type, the initial skin lesions take the form of hypopigmented or erythematous anaesthetic macules. Subjective manifestations are due to neural involvement and consist of numbness, tingling and formication (a type of paresthesia in which there is a sensation of ants crawling over the skin), and the skin may show burns or other lesions which the patient states are painless. It can be seen then, that leprosy is an important consideration in the differential diagnosis of syringomyelia and also of leucoderma. In the latter disease the differential point is that the hypopigmented areas are not anaesthetic, whereas in leprosy, the center of the macule is anaesthetic to light touch, pain, and temperature. Thickening of the peripheral nerves, especially the ulnar and peroneal, is also a common finding.

It is hoped that this brief excursion into the realms of medical geography will challenge the student to take an interest in the homelands of his patients, in their travels and in their personal histories. By doing so he broadens his own knowledge, and encourages the confidence and respect of his patients. He should try and keep a meneal note of those diseases based on his past experiences in clinical practice that were associated with persons from a foreign country. With this spirit of learning and constant enquiry, ehe praceice of medicine will be all the more exciting, and his value as a physician greatly enhanced.

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Cytomegalic Inclusion Disease

B. E. Koehler

Cytomegalic inclusion disease (C.I.D.) has assumed the status of what might be termed "an up and coming young disease" in recent years. The cellular lesions of the C.I.D. virus were originally described in 1904 by Jesionek and Kiolomengolou, and by Ribbert[1], as an incidental finding in the kidney tissue of fetuses suffering from congenital syphilis. The diagnosis of C.I.D. remained only a pathological one, however, until Smith first grew the viral agent in tissue culture in 1956, thus paving the way for the development of clinical serological tests.

AGENT

The cytomegaloviruses, also referred to as salivary gland viruses and cytomegalic inclusion disease viruses, constitute a group of cytopathogenic viruses of which there are at least three strains specific for humans, all having a common complement fixation antigen. The virus can be cultured in fibroblasts from human embryonic tissue. A group of viruses producing similar cellular lesions in lower animals has also been found, but these are not pathogenic for the human.

EPIDEMIOLOGY

C.I.D. is probably worldwide, but it occurs much more frequently as a subclinical infection than as a disease. Positive serological tests are found in 70% of infants at birth (cord blood), 15% of infants between 6 months and 2 years, 53% of adults between 18 and 25 years, and in 80% of adults over 35 years. (The high incidence of positive serology in newborns is probably explained by transfer of maternal antibody across the placenta). Clinical disease, in contrast, is infrequent, occurring in only 1-2% of infant deaths and very rarely in adults.

PATHOGENESIS

At present it is generally felt that infant infection is acquired "in utero" as the result of a symptomless viraemia of the mother occurring in pregnancy, during which the virus crosses the placenta. Quan and Strauss dispute the "in utero" theory of neonatal infection, quoting a series of 900 fetal and neonatal deaths in which only one death due to C.I.D. was found. They feel that this demonstrates the rarity of congenital infection and supports a concept of post-partum infection[4]. However, other studies have shown the development of disease within 48 hours of birth, which almost necessitates a congenital exposure to the virus[5]. Elek and Stern feel that the time of the maternal viraemia is important, and suggest the following chronological correlation:

(1) First trimester infection — abortion;

(2) Second trimester infection — congenital abnormalities;

(3) Third trimester infection — fulminant neonatal disease generalized in most tissues of the body, or localized salivary gland infection with no clinical disease[6].

Disease of older infants, children and adults is probably transmitted by objects contaminated by saliva, feces, or urine of infected individuals. However, it is also possible that such infection might be acquired "in utero" and remain latent in salivary glands or viscera until some precipitating factor later in life produces activity. Infection of older infants may, as in the newborn, produce a generalized, fulminating infection or subclinical infection localized to the salivary glands. In older children and adults nearly all infections are of the localized salivary gland type; disseminated disease is only found as a terminal complication of some other serious systemic disease. Subclinical infection in the older individual probably does involve some degree of generalization, but with the appearance of antibodies the infection becomes latent, and a delicate balance (like herpes) occurs, which may be variably affected by other diseases[6].

PATHOLOGY

In the infant the lesions of C.I.D. may occur only in the salivary glands, or, in the disseminated disease, they may be found in the kidney, liver, lung, ependyma of the lateral ventricles, and less frequently in many other tissues. Adult lesions are most commonly found in the lung, adrenals, gastro-intestinal tract, spleen, pancreas and kidney[7].

Lesions are mainly in epithelial cells in the infant. Those of the lung are located in the lining cells of the alveoli, while in the kidney the involvement of the epithelial cells of the convoluted tubules may cause swelling sufficient to produce obliteration of the tubular lumina. In the liver the epithelial cells of the biliary passages are involved. Ulcerations of the oesphagus,

stomach, and caecum may occur with gastro-intestinal tract involvement. Placental pathology is suggestive of erythroblastosis fetalis (pale, with increased size and correspondingly enlarged villi)[4]. In the adult lesions are mainly located in vascular endothelial cells and in macrophages. This suggests that there is some alteration in tissue susceptibility with age, which may be due to previous exposure producing a degree of immunity and, thus, a different response, or it may indicate the need of the virus to grow in more primitive types of tissue[7].

The microscopic cellular lesion is characteristic, regardless of the tissue or type of cell. In an enlarged cell (up to 40 microns) there are both intranuclear and cytoplasmic inclusions. The basophilic nuclear inclusion, containing numerous granular components and surrounded by a clear halo, is situated within an enlarged nucleus. The cytoplasmic inclusions are also basophilic, but are more finely granular; such inclusions tend to be crescent-shaped and located at the periphery of the cell. The inclusion bodies contain D.N.A. and probably represent masses of elementary bodies[3].

CLINICAL

By far the most important presentation of C.I.D. is as a disseminated infection in the neonate (frequently premature), with its high incidence of mortality and permanent sequelae. Active generalized C.I.D. produces a triad of hepatosplenomegaly, jaundice, and skin haemorrhages (petechiae, purpura or ecchymosis)[1]. Death may occur in 2-3 days or after some months; in the latter instance there develops increasing evidence of pulmonary involvement (interstitial pneumonia), hepatic insufficiency, and renal insufficiency. Occasionally massive haemorrhage will occur. Approximately one-quarter of such cases develop discrete areas of calcification around the lateral ventricles. If the infant should survive, other C.N.S. malformations may occur; specifically, micropolygyria, microcephaly, hydrocephalus, various forms of mental retardation, progressive uveitis with choroiditis leading to secondary optic atrophy, and motor disabilities, including spastic diplegia and epileptiform seizures[5]. Quan and Strauss quote a figure of 16% occurrence of such sequelae in a series of 76 cases of C.I.D.[4] However, the full range of C.N.S. involvement is not known, since recovery from the severe form is uncommon and since diagnosis was rarely made during life in the past.

Development of generalized disease in the older infant, usually occurring between 3 weeks and 3 months, produces a picture dominated by organ involvement and usually fatal within 3 weeks. The patient presents with diarrhea, vomiting, and evidence of upper respiratory tract infection, often in association with pertussis[3]. Such disease is uncommon over 4 months of age.

Infection in infants may, of course, be completely asymptomatic and limited to the involvement of the salivary glands. Such localized C.I.D. occurs as an incidental finding at autopsy in 10-12% of infants[7]. By far the greater proportion of adult infections are of the localized type, in salivary glands, G.I. ulcers, and lungs[7], and are completely subclinical. Such infection is widespread, as revealed by the increasing percentage of positive complement fixation tests with increasing age. Only very rarely is disseminated adult disease encountered (54 cases have been reported in the world literature), and then only as a secondary feature of the terminal stages of some other systemic disease, such as leukemia, malignant lymphomata, refractory anemias, ulcerative colitis[7], and as a complication of therapy with steroids, cytotoxic drugs, and antibiotics[3]. Most of these primary diseases are associated with a failure of bone marrow and/or reticulo-endothelial system, which produces a weakened body defence against infection. Diagnosis of such cases is usually made by surgical biopsy, since cytological methods are not tried due to lack of clinical suspicion[7].

DIAGNOSIS

The methods available for the diagnosis of C.I.D. prior to 1956 were only those of post-mortem examination of affected tissues. With the successful "in vitro" culture of the organism, it is now possible to utilize various serological tests, employing antigen prepared from tissue cultures by disintegration with ultra-sound. Cytological methods have also proved useful in infant disease since the affected epithelial cells tend to slough off and may be found by microscopic examination of centrifuged urinary sediment and gastric and bronchial washings. Such material may also be cultured. Percutaneous liver biopsy has been found to be a diagnostic aid, as has skull x-ray.

In summary, the diagnostic tests for C.I.D. are:

A. Post-mortem

   Giant cell inclusions in salivary glands, liver, kidney, etc.

B. Ante-mortem

   (1) Cytology

   (2) Skull X-rays (periventricular calcification)

(3) Virus isolation by culture

(4) Serology - complement fixation — neutralization tests

(5) Liver biopsy

These methods are by no means absolute. The virus has proved relatively labile in storage, so that sending urine specimens to laboratories for culture may prove a problem. (Shipping the specimens packed in wet ice has proved most satisfactory)[5]. Moreover, culturing requires weeks to months before there is sufficient yield to perform serological tests. The serological methods also have their limitations, for the serum probably represents a heterologous group of strains which cannot be distinguished and which may have a variable pathology. The complement fixation test has not always been positive on occasions when disease has been found to be present by other means. The wide dissemination of the cytomegalic viruses also complicate serological testing, for neonatal results may be confused by the presence of maternal antibody; even if a rising antibody titre is found, it may only mean clinically inapparent infection. A similar skull x-ray picture may be found in infection with toxoplasma gondii. It would seem that examination of cytology specimens or liver biopsy sections by a trained individual would prove to be the most reliable diagnostic methods.

DIFFERENTIAL DIAGNOSIS

A differential diagnosis is of importance only in disseminated disease of the infant, where a similar clinical picture may be seen with:

(1) Erythroblastosis foetalis;

(2) Sepsis;

(3) Toxoplasmosis;

(4) Congenital syphilis;

(5) Generalized herpes simplex;

(6) Congenital hemolytic icterus;

(7) Congenital leukemia[8].

TREATMENT

Specific treatment for C.I.D. is lacking at the present time, except for surgical removal of infected tissue — obviously impossible with generalized disease. A possibility for the future is the use of pooled human gamma-globulin.

CONCLUSION

C.I.D. is one of many diseases which is just beginning "to find its place in the sun". Although widespread in the community, it is almost entirely a latent infection in the adult population. (Some increase in the incidence of generalized adult infection can be expected with more frequent use of corticoids and cytotoxic agents). Its correlation with congenital malformations and with neonatal death necessitate positive action toward the development of prophylactic measures, especially as these relate to maternal infection.

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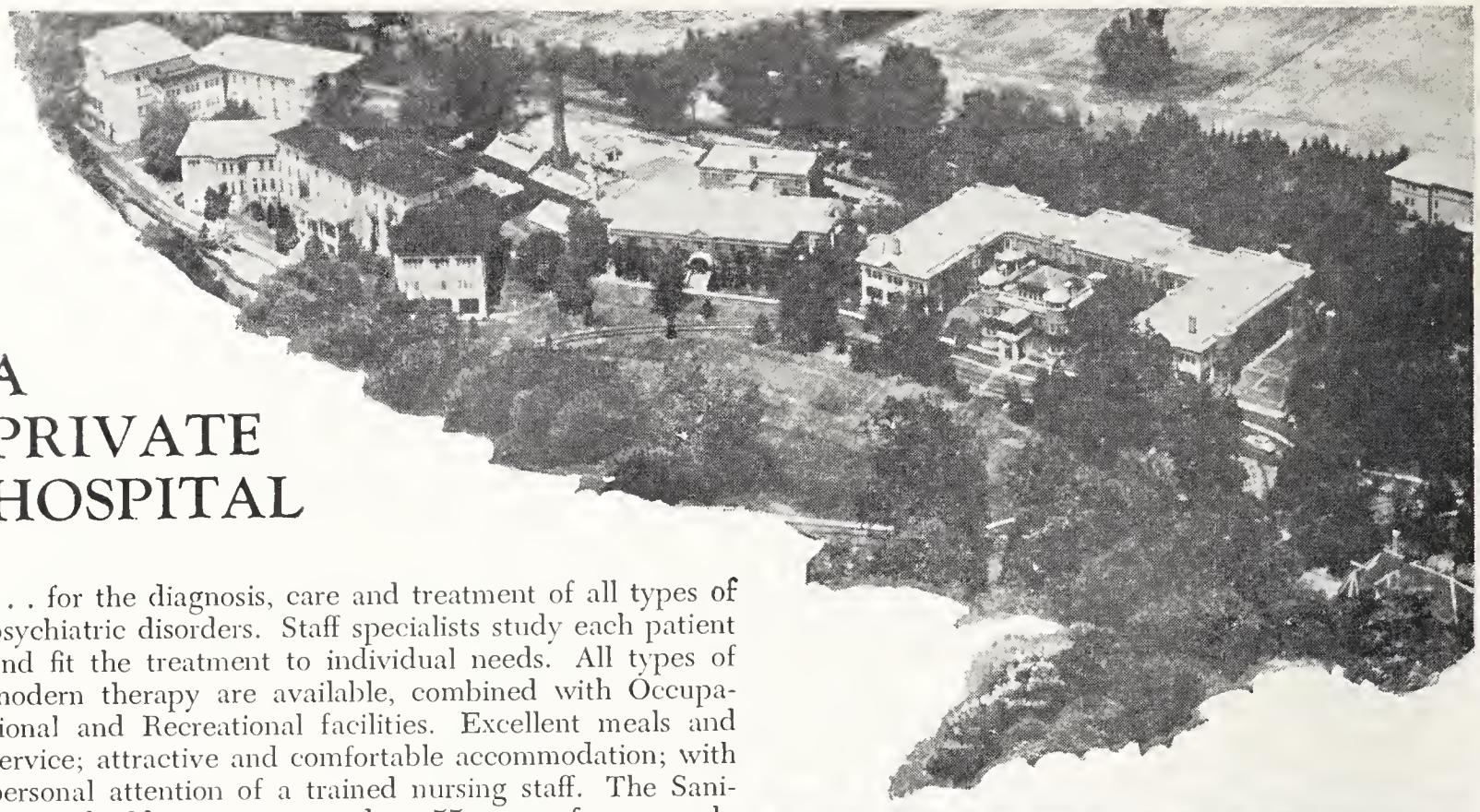

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Medical Horizons

When one considers the poor five year prognosis for staying single once out of school, and the relative ease with which borrowed money can be repaid soon after graduation, it is extremely enticing to take the opportunity after third year medicine to work in a remote part of the world — not only to see other places which may later be inaccessible, but to encounter varigated personalities and to come face to face with classical text book descriptions of many full-blown clinical pictures.

It was with these thoughts in mind that I decided last summer to seek a position in an underdeveloped country in Africa.

It was through the kind efforts of Dr. Schwenger of the University of Toronto Department of Public Health that I managed to secure a position in a Church Missionary Society Hospital in Eastern Nigeria. He had visited various parts of Africa just a short time previous to my request, investigating the advances being made in the field of Public Health, which is probably the most essential facet of medicine in all underdeveloped countries today.

Three days after my examinations were finished, I was off in the middle of the afternoon for Africa — by predawn the next day I had landed in Senegal. Two more stops and Nigeria was under my feet.

Stepping from the plane was like walking into a Turkish steam bath, but I was soon to learn that one accommodates very rapidly to that sort of humidity and temperature. My train ride from the airport to the Lagos University Hospital, where I was to spend four days with Dr. Fleming, an anaesthetist on staff at the T.G.H., (who is now finishing a two year hitch as acting professor of anaesthesia), was one of honest cultural shock. After all I had read, I still was not prepared for what I saw. Wooden shacks, mud huts with thatched roofs, goats running free all over, and little children roaming about with their only piece of 'apparel' being their umbilical hernias. There were thousands of adults walking in all directions, some with infants on their backs, some with tremendous loads on their heads, some arguing vehemently, some sitting by their houses or merchandise stands pounding out rhythms on drums or cardboard boxes, while others chanted or danced with laughing or serious faces. All of the adults were dressed in a splendid array of colours. I guess my special senses of sight, smell and hearing had never received so much stimulus in so short a period of time.

After spending four enjoyable days in Lajos seeing the modern hospital, meeting people, and introducing myself to long walks in the market, I left for where I was to spend the next nine weeks.

There I was, passing over steaming jungle, marvelling at the wonder of cities hacked out of this dense underbrush. The plane started to come down and the next thing I knew, we were landing on a clay runway. The superintendent of the hospital was there to meet me and we started a fifty mile car ride over a road not unlike those travelled in Algonquin Park. We spoke of the different conditions to be seen and treated here, the limitations of the hospital with reference to laboratory tests — most not going beyond the routine blood work, Kahn's, and stool tests for parasites — and naturally, the limitations of surgery.

At the hospital I was introduced to the other two European doctors, and to one Nigerian, Doctor Adimora, who, I learned later, was a graduate of Harvard University. Having been shown my quarters which consisted of a two room unit to myself among the junior staff of the hospital, I then asked whether it was possible to be shown about before 'Low Tea' — (British, you know) and this request was granted. There were two hundred beds. When a patient was admitted, either his wife brought him meals every day, walking sometimes six to ten miles round trip, or she brought the entire family to the hospital and set up 'house' in multiple family quarters set aside for this purpose. My first view of the beds revealed structures which were six to eight inches off the ground. I did not believe that the chickens which I noticed walking around on the loose outside could walk under them, but my doubts were dispelled a few moments later when in trotted three of the noble birds and squeezed under with ease. I guess though, the most surprising thing was that no one was at all alarmed or even surprised by their presence in the ward. I realized rather quickly, and was somewhat impressed by my astute powers of observation, that things were a little different out here. At any rate, one common denominator was that here too the patients were sick and in need of medical attention, which, in all fairness, was prescribed and given with excellent results, regardless of the lack of perfect facilities in the surrounding environment.

The schedule was such that on Monday, Wednesday, Friday and Saturday, the time was utilized by seeing outpatients from 7:00 A.M. until 7:00 P.M., being disturbed periodically by untimely presentations of

acute urinary obstruction, acute appendicitis, inevitable abortions, and rather acute falls from palm trees etc.

Throughout the first two weeks I sat with the other doctors as they dealt with the patients' histories, and through an interpreter made diagnoses and either admitted the patient into hospital or more usually treated him on an outpatient basis. Most of the problems encountered were malaria, amoebiasis, pneumonia, malnutrition, hemmorrhoids, venereal disease and tuberculosis. So frequent in fact is tuberculosis that once the diagnosis is made, these people are simply placed on combined therapy of Isoniazid and P.A.S. and seen later on an outpatient basis on special days.

Tuesday and Thursday were set aside for elective operations. There was one operating theatre in which the usual garb was worn, except that barefeet were preferred to any special conductive footwear. The scrub was done in the same room in tapwater from a sink. Most of the light during operative procedures was furnished by good old sol shining through the open windows. No, there was no chicken freeway through the operating room. The most astonishing aspect though, of all the operative procedures, was the low incidence of post-operative infection, which was almost nil.

Sunday was pretty well the day of worship, although naturally one of the doctors was always on call should an emergency arise.

The only obstetrics which came to the hospital were those mothers who had either had previous problems or those who had been diagnosed during the prenatal period as possibly being on the small side of a normal pelvis. If the labor went along satisfactorily, the midwife, a girl who had trained as a nurse and who had taken a year's training in addition in midwifery, would be in charge. If any difficulties were encountered, then the doctor would be called.

Once I got into the swing of things, I was put in charge of a twenty-eight bed gynecology ward where I booked and did D. & C.'s, biopsies, etc. On outpatient days I saw my own patients and was completely responsible for the diagnosis and treatment. Here I saw at least thirty patients a day, below one half of what any of the other doctors saw. I did all sorts of minor operations, such as incision and drainage of abscesses, (many cervical abscesses showed Z.N. stain positive organisms), felons, paronychia and broken limbs. I should add that the nearest X-ray machine was six miles away and although of low voltage, it was quite satisfactory for bone x-rays. I performed deliveries but only those indicating the need for forceps, for as the midwives would say, "A doctor shouldn't dirty his hands by handling these easy ones (i.e. normal childbirth)". But I guess that was just their diplomatic way of saying, "This is my job, now you go and tend to your own business". I shudder at the thought that the forceps deliveries performed were practically all high forceps. Every time I was called by maternity, I feared the consequences. I guess the most astounding tale in obstetrics while I was present, was the story about the woman who was in for an elective caesarian section after having lost her last child because of a ruptured uterus — "too deep in the bush!"

I was on call every third and fifth night and would summon the superintendent to my aid whenever I ran amiss or the problem presenting was just too great for me to handle. After sundown the only light was supplied by kerosene lanterns, wick variety. How vividly I recall that first cutdown I had to do at night.

During the day I spent my free time taking the bus or converted panel trucks to town six miles away, and wandering through the market, fighting for bargains, walking along the shores of the Niger River or just slipping off behind the hospital compound through the small villages and I imagine frightening many of the young boys and girls. During the evenings most of my time was spent with the Nigerian doctor who truly took me in as a relative, and so I guess I achieved that which was most important to me namely, meeting, talking, and becoming intimate friends with many Nigerian people. Certainly they are a group of people who are extremely kind, compassionate, sensitive and above all, capable of extending the warmest hand of friendship I have ever been offered.

As I write this, I admit that I have diverged to considerable length in all directions, and I possibly could have handled my story in far fewer words, but I seem to have so much more that I would like to say.

The hospital, though primitive in many respects (and I have obviously been too facetious in this aspect) serves a great purpose not only in the name of Christianity and the morality of the Western world, but in the great concept of medicine.

In summation, I would advise all those who can muster any possibility of ever pursuing a similar course to avail themselves of this opportunity. What it has done for me has not been to satisfy my original desires, but only to intensify them. I warn though, this may be a contraindication to such a pursuit.

B. H. McGrath 6T4

Human Toxoplasmosis

Jerome S. Burke

Since the first description of Toxoplasma gondii by Nicolle and Manceaux[1] from the Institute Pasteur in Tunis in 1908, there has been a rising interest in this organism and in its clinical manifestations. The name is derived from the Greek "toxon", meaning a bow arc, connating the lunate shape of the organism. The specific name gondii is derived from the name of the host, the gondi, being a small North African rodent.

AETIOLOGY

Toxoplasma gondii is a crescentic protozoan about three by six microns in size, and is stained best with Wright or Giemsa stain. On the basis of morphology and biology, this parasite does not fit into any of the presently accepted toxonomic groups of protozoa. It probably belongs in a separate classification along with some other odd organisms that have similar internal morphology revealed by electron microscopy.

Toxoplasma requires an intracellular habitat to proliferate. It is unique in that it may infect any mammalian or avian cell except non-nucleated erythrocytes. It appears to divide by simple longitudinal fission, but this process may be more complicated, involving development of two daughter cells within the wall of the mother[2]. The host cell becomes distended and rupture takes place, thus liberating toxoplasmas which again are able to infect new cells. Except for this mechanism, no special cycles, schizogony, or the existence of any intermediate hosts are as yet known[3].

Besides its proliferative form, toxoplasma exists as a cyst. In contrast to the fragility of the proliferative parasite, the encysted organism is tougher, can withstand digestive juices, and may be involved principally in transmission. It is believed that the cyst form can initate recurrent illness by release into surrounding tissues from rupture of a cyst wall and induction of a local hypersensitivity reaction to the antigenic material which escapes[4].

LABORATORY DIAGNOSIS

The most important test is the Sabin dye test based on the observation that toxoplasma from the peritoneal exudate of mice when incubated with normal serum for one hour at 37 degrees C., became swollen and deeply stained when alkaline methylene blue is added to the suspension. Parasites exposed to antibody-containing serum under the same conditions appear thin and distorted and are not stained when the dye is added[5]. Because the occurrence of toxoplasma antibodies in the general population is frequent, a diagnosis solely by serologic means requires demonstration of a change of the test result from negative to positive, from low titre to rapidly climbing titre or strikingly high stable titres such as 1:64,000 or greater[6].

Complement-fixing antibodies appear much later than those demonstrable by the dye test[7]. Because of this difference the special usefulness of the complement fixation test is in revelation of active infection when dye-test antibodies are already high and stable. A negative complement fixation test turning positive or high complement-fixing titres together with stable high dye-test titres are indications of active infection.

Jacobs[8] has described a haemagglutination test which employs a cell-free antigen. Titres seem to parallel those from the dye test, except that discrepencies are not infrequent with sera which have high titres by the latter procedure. Another new serologic procedure has been described by Goldman[9]. He measures antibody by their ability to inhibit a fluorescein-labelled antiserum from producing fluorescence in toxoplasma. This method is still under review.

The skin test reaction is of the delayed tuberculin type and appears late after acute toxoplasmosis. Because of delay, the skin test can be used as a primary screening procedure excluding acute toxoplasmosis from the diagnosis.

EPIDEMIOLOGY

Toxoplasmosis has been found in all orders of mammals, in some kinds of birds, and probably in some reptiles[6]. In man, serologic data indicate that in general: there is past exposure with increasing age; no sex difference; colder regions have less human infection than warmer areas; infection may be contracted in any season; and 33 per cent of the population of U.S. cities have positive serological reactions[10].

The mode of transmission is a puzzle. It may be due to the ingestion of toxoplasma cysts in raw or undercooked meat. The cyst wall is destroyed by digestive juices and the liberated parasites, unlike proliferative forms, can withstand digestion for one or more hours. But this data does not support the fact that vegetarians have been found to have positive serology in surveys in the United States and India[10].

CLINICAL MANIFESTATIONS

A. *Congenital*

Congenital toxoplasmosis occurs as an accidental complication (usually of an asymptomatic infection) of parasitaemia, in a woman who happens to be pregnant[11]. During the parasitaemia, an infected locus may be produced in the placenta permitting parasites to cross into the foetal circulation. If development of the placental lesion is delayed, then the passively transferred antibodies resulting from maternal response to infection might prevent seeding of the foetus by the parasite[12]. In contrast, if infection spreads rapidly, or if passive immunization of the foetus fails to occur, then the foetus would become infected.

Congenital toxoplasmosis may present itself in a variety of forms, from stillbirth to apparent normalcy at birth. Prematurity occurs in twenty-seven percent, with a mortality rate of twenty percent, as compared with seven percent for the full-term infant[12]. The newborn infant may be obviously abnormal with such evidences of active infection as hepatomegaly, splenomegaly, icterus, pneumonia, and a maculopapular rash. The majority of babies, however, show subsiding, if any visceral lesions, with active proliferation in the brain[13]. Subsidence of lesions indicates a degree of immunity generally passively acquired from the mother. The CNS lesions are of four kinds[14]: (1) necrosis of individual cells consequent to their parasitization with proliferating toxoplasmas; (2) tissue necrosis with microglial nodules following cyst rupture; (3) infarction necrosis of the cortex resulting from accidental vascular thrombosis; and (4) periventricular and periaqueductal vasculitis and necrosis, unique to neonatal human toxoplasmosis. Internal hydrocephalus, one of Sabin's[15] tetrad characterizing congenital toxoplasmosis (the others are convulsions, chorioretinitis, and cerebral calcifications) is the clinical sign associated with the peculiar periventricular lesion.

Hypothalamic lesions extending from the necrotic zone around the third ventricle may result in an unstable body temperature. The necrotic areas of the brain frequently become calcified with deposits visible radiologically, although not becoming striking until several months later[14]. Ocular involvement is almost always present in congenital toxoplasmosis and ophthalmoscopic examination for chorioretinitis with exudate in the vitreous is a useful aid in diagnosis[13].

Although generally fatal in the presence of hydrocephalus, less severe involvement of the brain does permit survival of the infant, usually showing residual chorioretinitis and cerebral scars. Major neurological sequelae of hydro or microcephaly, severely impaired sight, spasticity, palsies, and deafness are found to be more frequent in those children who present as babies with "neurological disease"[13].

B. *Acquired*

Because of the wide spectrum of clinical manifestations in acquired toxoplasmosis, the symptomatology is described below under the various organ systems[6]. Regardless of the severity, some or all of the various systems may be involved. The severity is probably the result of strain virulence and host susceptibility rather than of tissue tropisms of certain strains.

1. *Reticuloendothelial system*

Lymphadenopathy is probably the most common finding in the acquired disease[16]. The patient may seek aid because of "swollen glands". These nodes are discrete and may vary in their firmness; they may be tender. This finding alone, or in combination with involvement of other systems, may stimulate infectious mononucleosis[17]. The most common groups involved are the cervical, suboccipital, supraclavicular, axillary and inguinal.

The liver and spleen are both invaded early in the acute infection resulting in scattered focal areas of necrosis. In later stages of infection these lesions may be healed, with no particular histological changes evident. Either or both may be enlarged, and splenomegaly may persist beyond the acute and subacute stages of the infection.

2. *Lungs*

The signs and symptoms of atypical pneumonia may develop at any time during the course of the disease. Depending on the severity of the case, these may be minimal or very marked. The lung involvement may be the presenting symptom and may be the primary cause of death.[18]

The parasites invade and destroy alveolar cells resulting in an intense interstitial infiltration by inflammatory cells and a gelatinous exudate in the alveoli. A hyaline membrane coating the alveolar walls may be present. In less severe cases, foci of congestion may be noted.

X-ray findings may include accentuation of hilar lymph nodes, with spotty or coalesced areas of increased density.

3. *Heart*

Myocarditis is a common finding in the severe in-

fection.[19] In the acute stage, the myocardium is invaded by the parasite, and focal inflammatory lesions are produced. In later stages, the presence of cysts without any cellular reaction can occur. ECG changes have been seen in a few cases.[19]

4. *Musculoskeletal*

Toxoplasma invades and proliferates in many different groups of skeletal muscle. Myalgia and arthralgia may be presenting symptoms or may appear later. These, together with fever and chills, may simulate influenza. The myalgia may be relieved by simple analgesics and such attacks may be spaced days apart or may be continuous.

Muscle biopsy has been a successful means of diagnosis, both by microscopal demonstration and by isolation of the parasite.[13]

5. *Brain*

As stated earlier, the most severe involvement of the brain has been seen in the congenital disease. However, a few cases of acquired toxoplasmosis have shown encephalitis and fever as the principle symptoms.[18] Although such striking signs and symptoms are not commonly seen in adult infections, there may be considerable involvement of the brain in some cases. Calcifications, the evidence of healed necrotic foci in congenital cases, have not been found in association with the disease in adults.[14]

In the mildest form, headache may be the only symptom. In severe cases, there may be personality changes and the patient may present as a psychiatric problem. Meningoencephalomyclitis is sometimes present.

6. *Eye*

Acquired ocular toxoplasmosis seems to be a result of chronic infection. It may be a residuum of congenital infection. In the United States it is estimated that thirty-five percent of cases of posterior uveitis or chorioretinitis are due to toxoplasma.[20]

Active lesions appear as white or yellowish foci on the fundus. These have elevated oedematous margins, which are surrounded by a hyperaemic zone. Strands of fibrinous exudate and cells may be present in the vitreous, obscuring the fundus. Older lesions appear as glial scars and areas in which the retina has been destroyed, and choroid and sclera are visible. Around these depigmented areas, there is a deposition of pigment from the destroyed retina. The choroidal vessels may traverse the base of the lesion.[7]

In congenital toxoplasmosis the lesions are usually bilateral. In the adult disease only one eye may be involved. The position of the lesion may be perimacular as it frequently is in children, or peripheral.

In adults, depending on the position and activity of the lesion, the patient may present marked loss of central vision due to a perimacular lesion, or hazy vision due to accumulated exudate from peripheral foci.

Associated signs and symptoms may include perilimbal injection, pain, photophobia and epiphora. Cells, flare, and keratic precipitates may appear in the anterior chamber.

7. *Integument*

A maculopapular rash occurs in most severe cases.[6] This covers most of the body but spares the scalp, the palms, and the soles of the feet. The lesions may coalesce and appear as purpuric spots. In milder cases the rash may be very slight and transient. The rash has usually been found to appear during the first week of illness and to last for one or two weeks.

To summarize acquired toxoplasmosis three cases from the literature illustrating three different types of clinical syndromes are described:

Case 1 (*mild lymphadenopathy*[16]). A 12-year-old girl, apparently healthy, was admitted to the hospital for observation for an oligophrenia of about 9 years' duration. On admission there were no complaints, and the temperature was normal. On the neck, body and proximal parts of the thighs, the remains of exanthema were seen. Except for a left-sided strabismus, no abnormal signs were present, particularly no respiratory, cardiac, muscular or neurologic signs. There was no enlargement of the liver or spleen. The preliminary diagnosis was oligophrenia, and, on routine examination for toxoplasmosis (carried out at that time on all neurologic and psychiatric patients), positive seroreactions were revealed. At the same time, on renewed examination, lymph nodes the size of cherries were found in both axillae, and lymph nodes the size of peas in the groin. There was no adenitis in the neck. The lymph nodes were smooth and mobile, and were covered by normal skin. To confirm the serologic diagnosis, a lymph node in the right groin was excised about 1 month after admission, and, 4 months later, a lymph node was also removed from the right axilla. In both cases toxoplasmas were isolated by injection of a lymph node suspension intraperitoneally into mice.

Case 2 (*"glandular fever"*[16]). A 20-year-old female, previously asymptomatic, discovered a tender swelling

in front of the left ear. Because this increased in size during subsequent days and a similar swelling occurred in front of the right ear, she was admitted to the hospital with a diagnosis of adenitis. She felt unwell and feverish, but otherwise there had been no symptoms. At the time of admission the temperature was 100°F. Examination showed nothing abnormal, except for redness of the fauces and lymphadenopathy. There was swelling of the occipital, preauricular and cervical lymph nodes. These were the size of hazelnut kernels and were smooth, firm, uniform and freely mobile, but *tender*. There were no respiratory, cardiac, muscular or neurologic signs, no enlargement of the liver or spleen and no exanthema.

The preliminary diagnosis was acute pharyngitis and adenitis. Because of the demonstration of *lymphocytosis with atypical cells,* accompanied by a negative Paul-Bunnell test, seroreactions for toxoplasmosis were carried out, with positive results (dye test, 1:6250).

The temperature became normal in 3 days. In spite of this, the lymphadenopathy increased. Twenty-two days after the onset of the disease, tender lymph nodes were found in both axillae and groins. Except for pronounced fatigue, there were no complaints at the time of discharge 20 days after the onset of disease.

On follow-up examination 2 months after discharge from the hospital the lymph nodes that were previously affected showed no change, and, in addition, new, very tender nodes were found along the left border of the trapezius. Five and a half months after the recognition of the lymphadenopathy, the patient still felt tired, but was able to carry out her work. The tender, enlarged lymph nodes still persisted. A lymph node was removed from the left occipital region, and toxoplasmas were isolated.

Case 3 (*exanthematous pneumonitis and encephalomyelitis*[18]). A 43-year-old woman entered the hospital complaining of fever, cutaneous rash and increasing weakness. Two weeks previously she noted a feeling of weakness and malaise that continued for 10 days. Six days before admission she experienced a chill, followed by a sudden rise in temperature and a severe headache. The temperature remained elevated and on admission was 106.6°F. On the day of admission marked cyanosis, with nausea and blurring of vision, developed. A dry, nonproductive cough was present.

Significant physical findings were an erythematous maculopapular rash covering most of the body, but sparing the palms of the hands, the soles of the feet and the scalp. The abdominal viscera were not palpable, and neurologic examination was negative.

The clinical condition remained the same during the first four days in the hospital. Five days after admission, cyanosis, marked dyspnea and tachypnea suddenly developed. Rales were heard at both lung bases posteriorly. X-ray study showed a pronounced accentuation of the hilar shadows and lung markings of the lower lobes, suggesting pulmonary congestion. The cardiac shadow appeared normal.

Eight days after admission, the patient became irrational. Respiratory difficulty continued. At this time all normal reflexes of the lower extremities and abdomen were absent, and a positive Oppenheim reflex was elicited. There was no neck rigidity.

The temperature remained high, averaging 103 to 104°F. throughout the course of the illness. There were transitory remissions at irregular intervals, but rarely did the temperature approach normal. Terminally the patient's hearing became very poor. She died 12 days after admission.

Laboratory work-up during the course of the disease was not remarkable. Toxoplasma was found in microscopical sections of the lung, spleen, liver, skeletal muscle, heart muscle and brain. The organism was isolated from normal animals inoculated with citrated blood of the patient obtained 2 days before death, or with triturated brain tissue after death.

Treatment

The treatment of choice is the combined use of Sulphadiazine and Pyrimethamine (a substituted phenylpyrimidine antimalarial drug) which act synergistically against toxoplasma.[16] However the parasite is not always eliminated by such treatment. The ability of the drugs to effect a radical cure is apparently related to the time during the course of the infection when treatment is initiated as well as to the strain of parasite involved.

Cases of chorioretinitis characterized by a series of flare-ups and spontaneous remissions may be due to the rupture of cysts, liberating parasites into sensitized tissue. Pathogenesis here, may be a hypersensitivity reaction rather than due to proliferating organisms. With this rationale, chemotherapeutic control of such ocular disease would require in addition to the above antitoxoplasma drugs, steroid therapy to reduce the inflammatory response.

Recently, Trypacidin, a new antibiotic active against toxoplasma, has been described.[21] However, its clinical effectiveness is still under review.

The past decade has witnessed the emergence of

toxoplasmosis from a biological and clinical curiosity to a subject of extensive research and clinical interest and importance. Experimentally, it is an excellent model for the study of intracellular parasitism and tissue specificity. Clinically, it poses an increasing challenge as a cause of congenital and acquired disease.

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Abstracts

A Hypernephroma Associated with Elevated Levels of Bladder Carcinogens in the Urine: Case Report, W. K. Kerr, et al. Br. J. of Urology, Vol. 35, No. 3, p. 263, 1963.

The patient described in this report was a 62 year old man with a history of good health and painless hematuria of two days' duration. Clinical studies suggested the diagnosis of carcinoma of the left renal pelvis.

It is known that certain chemicals may be the cause of bladder tumors. Moreover, certain tryptophan metabolites may be the carcinogens in certain "spontaneous" bladder tymors. This patient was given oral tryptophan and urine tryptophan metabolites followed; the carcinogens were found in a concentration 4x normal. At operation a small hypernephroma (the smallest ever removed at TGH) was removed. The authors speculate on the possibility of the production of this tumor being due to endogenous carcinogenic agents.

Islet Cell Carcinoma of the Pancreas Producing Obstructive Jaundice: P. E. Kalish, et al. *Annuals of Surgery,* Vol. 158, p. 222, 1963.

The authors describe a case of non-functional islet cell carcinoma. These lesions are classified according to their malignancy and presence of insulin production; they usually involve the body and tail of the pancreas. Generally they develop rapidly, metastasize readily and carry a poor prognosis. There are, however, exceptions to this as shown by the case in point.

The patient presented with signs and symptoms of biliary tract obstruction and, although several operations were performed, excision of the primary tumor was never carried out. Indeed, the primary appeared benign and was diagnosed through the histology and effects of the secondaries.

Despite metastases some islet cell carcinomas allow a long survival, in the case of this patient, 17 years. Similar cases are on record.

Landmarks

"Tobacco As A Remedy in Otalgia is extolled by Dr. Thomas C. Osborn in the New Orleans Med. and Surg. Journal. The cases in which he resorted to it, were mostly neuralgic, due to malarial influence. The first case in which Dr. Osborn resorted to it was in a little girl in the second or third hour of a quotitien paroxysm of otalgia. The mode of application was very primitive and probably will not be adopted generally in practice. It consisted simply of conveying a quantity of the doctor's saliva saturated with tobacco into the patient's ear. In a few moments, the patient was quiet, free from pain, and soundly asleep. The local use of tobacco in ear-ache has since passed into the hands of the people in the doctor's neighbourhood as a very efficient remedy.

Dr. Osborn also speaks very favourably of local applications of tobacco in cases of prurigo preutii preputii, scroti, podicis, and pudendi mutietsris.

Br. Med. J. p. 482
April 27, 1867

Purses in Hospitals

The police reports of Monday last tell us that a "respectable tradesman's wife of Dartford" was taken up for pocket-picking in Guy's Hospital. We notice the incident because it illustrates the style of patients who improperly obtain gratuitous medical services at our public charitable institutions. This "respectable wife" appears to have found the patients' waiting-room a good field for the exercise of the gentle craft of picking pockets. Clearly the patients were of a class who have well lined pockets. Many of them complained that their purses had disappeared. It does not seem to have occurred to any of these respectable females with purses in their pockets that they were robbing the doctor by improperly obtaining charitable aid. The facility with which gratuitous medical aid is obtainable at our hospitals, is one of the evils to which we have frequently called attention. It is very necessary to devise some system of checking the abuses festered by the out-patient system. Gratuitous services are rendered by no other profession in the same proportion as in ours. At least the medical men in the hospitals, and the profession at large, should be protected from abuses of their charity by well-to-do persons.

Br. Med. J. p. 296
March 16, 1867.

The Gain in the Average Duration of Human Life.

Dr. C. A. Logan, in his Report on the Sanitary Relations of the State of Kansas, cites the example of Geneva in Switzerland, where an accurate record of the population, births and deaths has been kept for more than three centuries past or since the year 1560. By a series of historical and statistical computations, M. Mallet has ascertained that from the year 1530 to the year 1600, the mean duration of the lives of the people was, in round numbers, twenty-one years and two months. During the seventeenth century, the mean life had increased to twenty-five years and nine months; and in 1833 it had reached forty-five years and five months, being nearly double what it was two centuries before. This result was brought about by a most salutary regulation of the public health, through which much of the former unnecessary sickness was prevented.

Br. Med. J. p. 231
March 2, 1867.

Abstract

The Treatment of Shock accompanying Myocardial Infarction: A. Bernstein, et al. *Angiology, 14,* No. 11, November 1963, 559-563.

Untreated shock in myocardial infarction has a mortality of 80-90%. Although it is known that there is reduced stroke volume, tachycardia and peripheral vasoconstriction, factors governing these are not well understood. Principles of therapy are concerned primarily with increasing cardiac output and coronary blood flow to alleviate myocardial and cerebral hypoxia.

Various means are available to do this but the most useful in everyday practice is the use of pressor amines. Many of these have been suggested or are in use and the authors bring forward another, mephentermine, which they consider superior in many ways to some of the other drugs suggested. In the article they discuss the reasons for their choice.

Parasitic Diseases

L. Schwartz

Introductory Remarks

There is a common misconception among medical students and doctors on this continent that parasitic diseases occur only in the deepest jungles of Africa, South America and India and are not a problem in North America. This may have been true twenty or thirty years ago but today with increased immigration and travel to both tropical and European countries more and more people infested with worms are filtering through our out-patient clinics and private practices. At the Toronto General Hospital twenty-five cases of parasitic infestations have been diagnosed at its medical outpatient clinic in the last five years and it is estimated that this number is greater than the number of cases of Hodgkin's Disease or Pernicious Anemia seen at the clinic during the same five year span.

Therefore the emphasis in this paper will be on the clinical features and methods of diagnosis of the commoner parasitic diseases seen here. Reference will be made continually to cases seen at our clinic because they represent typical ways in which these diseases present in North America where worm infestation is not considered commonplace and where patients will seek medical attention before they are beset by some catastrophic symptom such as bowel obstruction. This latter occurrence, I have been told, is not rare in tropical countries.

A simplified classification of the parasites dealt with in this paper is shown in figure #1. This has been included for the purpose of orientation and is by no means complete.

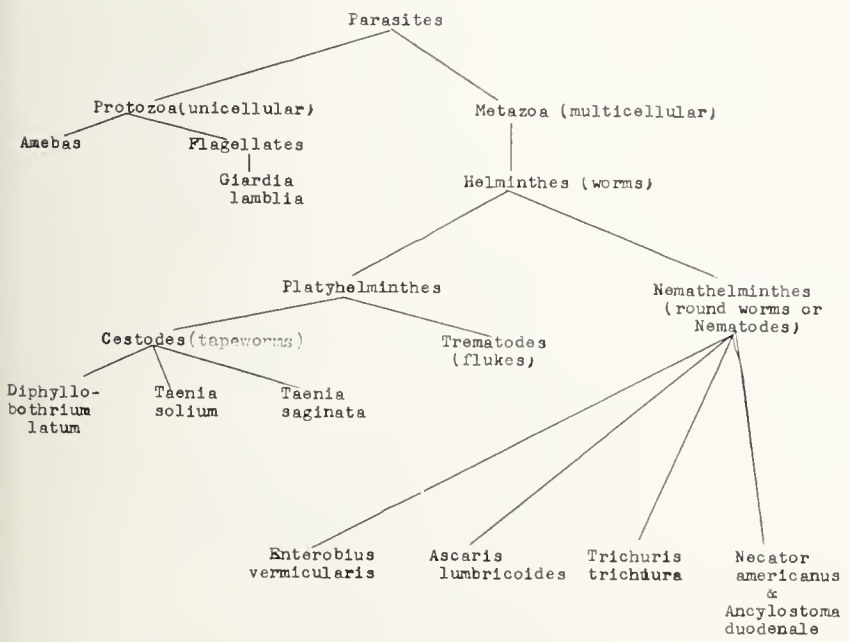


Figure 1. A simplified classification of parasites discussed.

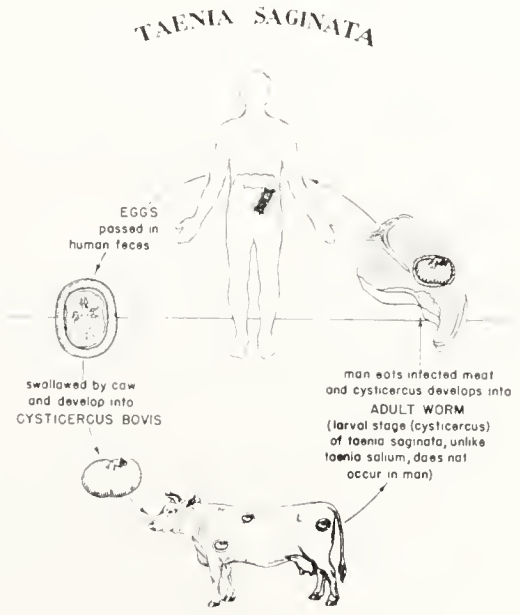
Eight parasites will be dealt with under the following headings: distribution; life cycle; clinical features; diagnosis; treatment. Only the most general aspects of the last will be presented; for a more comprehensive description of treatment the reader is referred to Dr. Lenczner's paper (Refer to bibliography).

The Cestodes or Tapeworms

A tapeworm consists of a chain of segments with a head (or scolex) with which to attach itself. Behind the head is a narrow neck which grows forming segments which are continually pushed back; each segment is called a proglottid. Thus, the proglottids just behind the neck are the youngest but as they move back there is gradual development of internal organs with the terminal segments filled with a pregnant uterus and large numbers of eggs. Each proglottid thus possesses complete reproductive organs of both sexes with fertilization within a segment being most common. The cestodes have no definite digestive system and survive by absorbing digested but unassimilated food from the fluid intestinal contents in which they live.

1. *Taenia saginata* (or beef tapeworm)

Distribution It is very common in Africa (especially Ethiopia), Tibet, Syria, Central & South America where the meat is cooked so that only the surface is broiled while the interior containing the cysticercus (the larval form) is only warmed.


TAENIA SAGINATA
EGGS passed in human feces
swallowed by cow and develop into CYSTICERCUS BOVIS
man eats infected meat and cysticercus develops into ADULT WORM (larval stage (cysticercus) of taenia saginata, unlike taenia solium, does not occur in man)

Clinical Features The symptoms if any are very non-specific and in fact the two patients who presented at our clinic with beef worm infestation came be-

cause they noticed segments in their stools. In retrospect symptoms included anorexia, vomiting, constipation, epigastric pain, dizziness and fatigue. A diagnosis could not be made with these presenting symptoms unless one can teach oneself to be suspicious when an Ethiopian, for example, presents with vague gastro-intestinal complaints but has no physical findings, and to do a stool examination in all such cases.

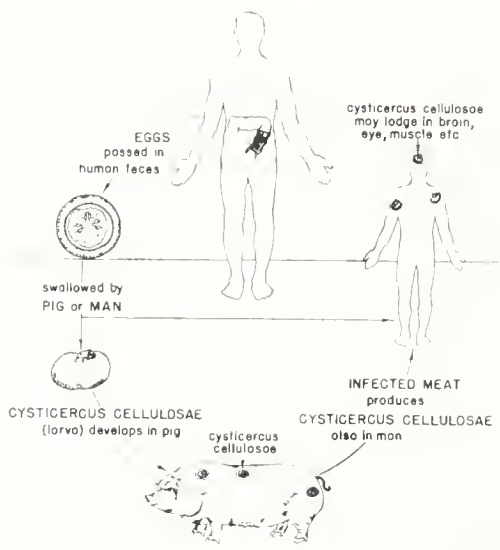
Diagnosis Ova can be identified in the stools but these eggs are indistinguishable from those of Taenia solium. Therefore, definite diagnosis depends on the recovery of the distinctive scolex or proglottid.

Treatment In general this consists of the ingestion of Atabrine tablets preceeded and followed by saline purgation. Definite success of treatment depends on the liberation of the scolex for if it has not been removed regeneration of the tapeworm will occur and retreatment will be necessary within two months. Thus, the stools should be examined carefully.

2. *Taenia solium* (pork tapeworm)

Distribution It is common where pork is eaten without thorough cooking especially in Mexico, Central and South America, North China, Manchuria and India. It is rare in North America and in countries inhabited largely by Moslems and Jews, religions which forbid pork ingestion.

TAENIA SOLIUM



It is noteworthy that the cysticercus form can develope in man either by ingesting eggs directly by anal contamination of the fingers or by hatching of the eggs liberated in the intestine and propulsion of the released oncospheres into the stomach.

Clinical Features A case which presented at our clinic exemplifies the problems in diagnosis which may be encountered with this worm. The patient was well until she suddenly developed epileptic attacks both grand mal and psychomotor in type. Attempts to control these seizures with the usual therapeutic agents were unsuccessful. Soon puffiness and pain of her right hand began to bother her. The electroencephalogram revealed focal temporal lobe activity and multiple intramuscular calcifications were present on X-rays of the limbs. The electrocardiogram was compatible with mycardial damage possibly due to the parasite. In this case as undoubtedly in many, the initial nonspecific general and gastrointestinal symptoms which are characteristic of tapeworm infestation, either did not occur or were not severe enough to alarm the patient or her doctor if indeed one was sought at this stage. These symptoms however are significant and are danger signals of possible future invasion of the larval form into the muscles and viscera including the heart and brain. One can certainly be excused for missing the diagnosis at the early preinvasive stage but convulsions should never be written off as idiopathic until limb X-rays as well as skull X-rays are done.

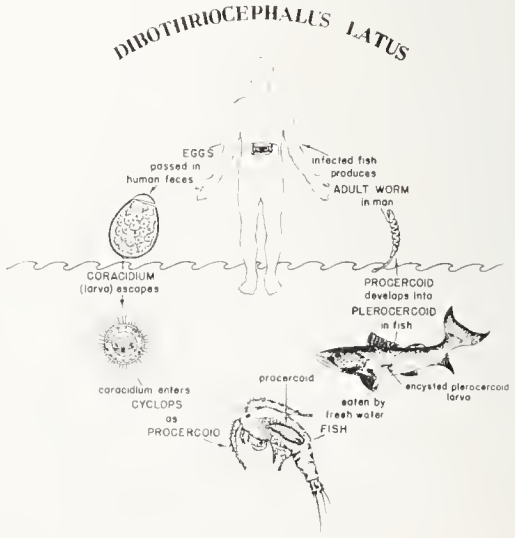
Diagnosis The ova are indistinguishable from Taenia saginata and also are not always present in the stools; therefore, diagnosis depends on the identification of the characteristic scolex and proglottids.

Treatment The treatment of the intestinal worm is the same as that of Taenia saginata. The only possible treatment of cysticercosis of the brain is removal of the larval cyst surgically.

3. *Taenia Diphyllobothrium latum* (fish tapeworm, Dibothriocephalus latus)

Distribution This worm is of some importance to inhabitants of the Great Lakes area because it is reported that 50-75% of the pike and pickerel in these lakes harbour larvae. Millions of pounds of fish are annually imported from infected Canadian lakes for the preparation of gefullte fish and many cases develope in Jewish women when they taste the fish during its preparation before it is thoroughly cooked. Fish tapeworm is also particularly prevelant in Finland where 20% of the population are infected and in local areas in the Baltics where nearly 100% harbour the worm.

DIBOTHRIOCEPHALUS LATUS



Clinical Features In most cases there are no symptoms or at the most the vague gastrointestinal complaints typical of tapeworm infection; patients usually seek medical aid because they notice segments in their stools. However, occasionally a patient may present with a macrocytic hyperchromic anemia which is refractory to Vitamin B_{12} therapy and stool examination reveals ova and fish tapeworm proglottids. The developement of this anemia is due to the capacity of this worm to absorb 10-15 times as much Vitamin B_{12} as other tapeworms. Treatment of this anemia with B_{12} is fruitless unless the tapeworm is first eradicated.

Diagnosis The Diagnosis is made by demonstrating the characteristic proglottids in the stools.

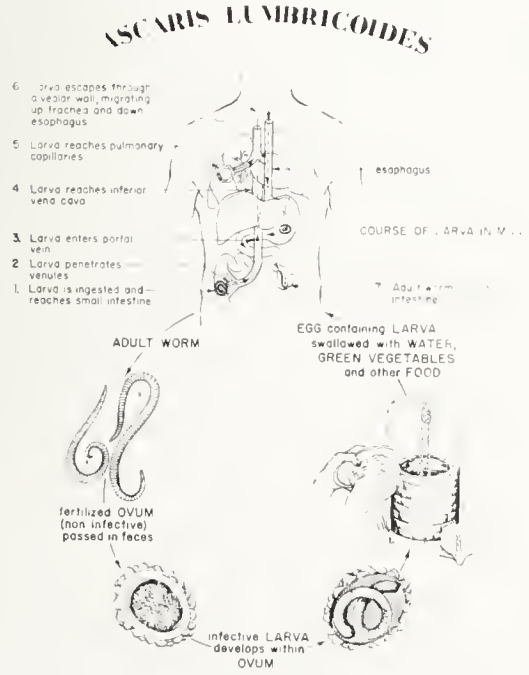
Treatment The treatment is the same as that of Taenia saginata.

THE NEMATODES OR ROUND WORMS

The nematode is an elongated, cylindrical worm tapering at the head and neck and encased in a tough, impermeable, transparent or semitransparent cuticle which is marked externally by fine transverse striations. In contrast to the tapeworms, the sexes are separate with the males smaller than the females.

1. *Ascaris lumbricoides* (round worm)

Distribution Infection is world wide but thrives particularly well where there is abundant moisture and shade and also under conditions where hands and food are contaminated by eggs developing in the soil and in the floors and dooryards of huts polluted by young children. Ascaris therefore is common in India, Egypt, Panama, China and in the southeastern U.S. (particularly southern Louisiana).


ASCARIS LUMBRICOIDES
6 Larva escapes through alveolar wall, migrating up trachea and down esophagus
5 Larva reaches pulmonary capillaries
4 Larva reaches inferior vena cava
3 Larva enters portal vein
2 Larva penetrates venules
1 Larva is ingested and reaches small intestine
esophagus
COURSE OF LARVA IN M...
Adult worm intestine
ADULT WORM
EGG containing LARVA swallowed with WATER, GREEN VEGETABLES and other FOOD
fertilized OVUM (non infective) passed in feces
infective LARVA develops within OVUM

Clinical Features Ascaris can produce symptoms due to either of the stages of its life cycle which occur in man. In the preintestinal phase migration of the larvae through the lung may cause hemorrhage and severe pneumonia if infection is heavy. In the intestine the worms may be so numerous and bulky that they cause intestinal obstruction, or appendicitis (if they accumulate in the region of the caecum). In one of three cases of Ascaris at our medical clinic abdominal pain was so severe that an exploratory laporotomy was necessary and the surgeon was amazed to find round worms blocking the ileum. The other two cases presented much less spectacularly with abdominal pain and tenderness and anorexia. Due to the wanderlust of Ascaris other symptoms are unpredictable; for example, if the worm crawls up the bile duct, biliary colic may result; if it journeys back into the stomach, it may be vomited up.

Diagnosis The diagnosis is made by demonstrating the characteristic eggs in the stools or the identification of an adult worm or immature worm that is passed spontaneously or vomited.

Treatment Piperabine citrate: — 150 mg per kilogram body wt. is used and repeated in one week. Stool examination for ova is done after the second dose and if it is still positive treatment should be repeated. If eradication of the worm has still not occurred alternative therapeutic agents such as Hexylresorcinol or Serotonin can be tried.

2. *Hookworm* (Necator americanus and Ancylostoma duodenale)

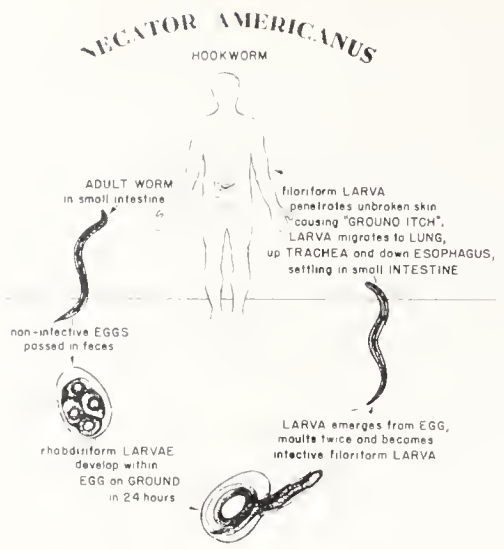
Distribution (and *Incidence*) Probably one quarter of the world's population is infected by this worm. In this continent it is most prevelant in the southeastern United States. In assessing the likelihood of the presence of hookworm infection in a particular patient, the following facts may be helpful:

(1) age; the highest incidence is between the ages of 15 and 19

(2) occupation; infection is more common in agricultural workers and miners.

(3) climate; rainfall is an important factor with infections never common in areas with less than 40 inches of rainfall

(4) defecation habits; these also play a part since infection may be acquired while standing barefoot in previously polluted ground; thus, the wearing of shoes tends to prevent infection.



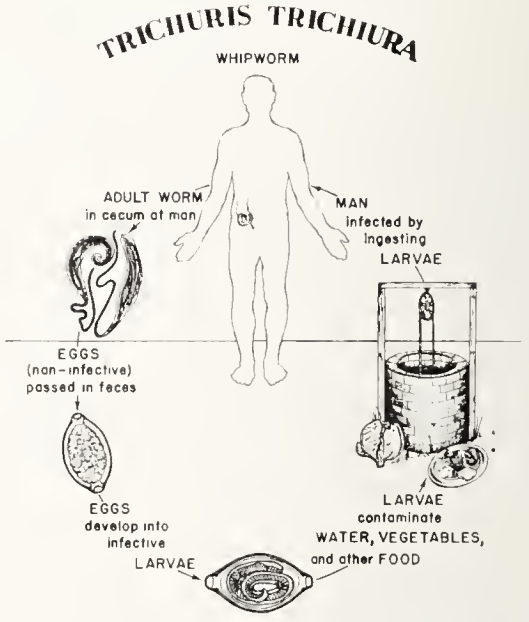
Clinical Features The preintestinal symptoms including pruritis and inflammation of the skin as well as pulmonary infection although described as characteristic of hookworm infection did not occur in any of our five cases. As the worms are maturing in the intestine there may be nausea, abdominal discomfort and diarrhea. More important, however, are the symptoms of anemia which appear due to the constant sucking of blood by this worm. If the diet is nutritious with more than adequate amounts of protein and iron, then the signs of anemia will be delayed and in a mild infection may never occur; by the same token, if the diet is borderline then a minimal infection will lead to an iron deficiency anemia. The anemia leads to pallor, fatigue and other typical signs. It should be emphasized that in contrast to the vitamin B_{12} deficiency anemia which follows fish tapeworm infection, hookworm anemia is by no means uncommon; this was the presenting finding in four out of the five patients in our clinic and in two of these the correct diagnosis was entertained only after prolonged but unsuccessful iron therapy. In children protein deficiency as well as iron deficiency may complicate the picture leading to weight loss or failure to thrive; there may also be mental retardation and emotional disturbances in such children. Infection in pregnant women leads to a number of stillbirths due to the unmet demands of the foetus for iron and protein.

Diagnosis A positive diagnosis can be made only by finding eggs in the stools.

Treatment Tetrachlorethylene is used followed by a saline purgative. Stool examination is done after one week and if stool examination is still positive for ova or larvae, treatment is repeated in two weeks.

3. *Trichuris trichiura* (whipworm)

Distribution It is a common inhabitant of the cecum and large intestine of many animals and as such is world wide. As a human infection it is common in the moist parts of warm countries and in North America it is located where there is dooryard pollution, dense shade or heavy rainfall (in southwestern Louisiana and the southern Appalachians). Children are often infected.



Clinical Features As with most parasites, light infections are symptomless and the presence of the worm is discovered on routine stool examination. However, three of the 4 cases that presented at our clinic had very definite symptoms. Two of the patients had definite abdominal pain along with various constitutional symptoms including loss of weight and appetite and diarrhea. In one of these cases there was hepatosplenomegaly; in the other, splenomegaly. Apparently the abdominal pain in this disease may be so severe as to simulate appendicitis although this diagnosis was never contemplated in these two cases. The third case presented with typical signs of anemia and a haemoglobin of 8 grams%; this is in keeping with the blood sucking tendency of whipworm; the liver was enlarged in this patient and there was also jaundice. The hepatomegaly and splenomegaly observed in these cases are not part of the usual description of whipworm infection; it is difficult to determine whether or not these are incidental findings or due to Trichuris (possibly this worm also crawls up the bile duct).

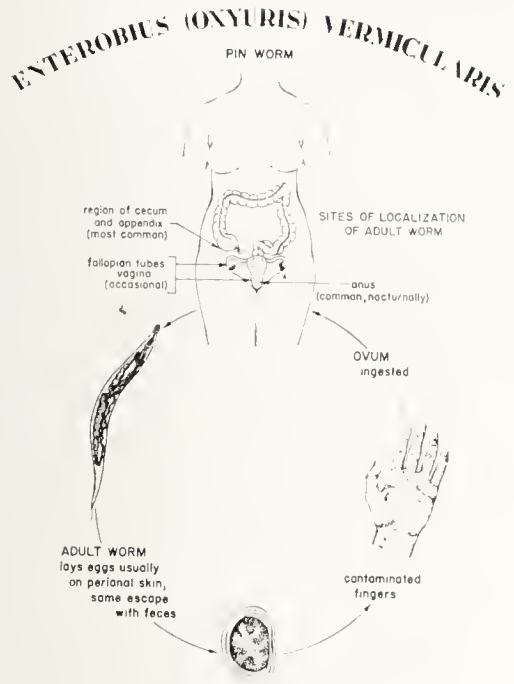
Diagnosis Demonstration of ova in the stools often requires stool concentration.

Treatment Dithiazanine iodide is the preferred drug in the treatment of whipworm.

4. *Enterobius vermicularis* (pinworm; seatworm; threadworm)

Distribution It is worldwide in distribution but is rare in the tropics and the coloured races are less susceptible. On the other hand, it is reported that 30-60% of white children in the United States and Canada are

infected; the high incidence in children is accounted for by the fact that the anus to mouth transfer of eggs is more likely in this group.


ENTEROBIUS (OXYURIS) VERMICULARIS
PIN WORM
region of cecum and appendix (most common)
fallopian tubes vagina (occasional)
SITES OF LOCALIZATION OF ADULT WORM
anus (common, nocturnally)
OVUM ingested
ADULT WORM lays eggs usually on perianal skin, some escape with feces
contaminated fingers

Clinical Features The immature worms tend to localize around the caecal region and may lead to obstruction of the appendiceal lumen and resulting appendicitis. More commonly however, patients complain of perianal pruritis which may be severe enough to lead to emotional upset. In female patients the worms may continue their nocturnal journey past the anus and find their way into the vagina thus producing a vaginitis.

Diagnosis Direct faecal smears detect less than 1 per cent of infections because eggs are seldom in the faeces. Therefore, a scraping of the perianal region is necessary; the scotch tape method is best; a piece of scotch tape is held at the end of a tongue depressor and applied to the perianal fold and then flattened on a slide. Occasionally the adult female worm will be observed crawling in the anal region or in the faeces; remember, however, never to rely on the observations of an anxious individual who may mistake a harmless vegetable fibre for a worm.

Treatment Antepar is given once daily for seven consecutive days; then starting one week after the completion of treatment seven consecutive perianal transparent cellophane swabs are taken in the early morning on rising; each of these must be free of Enterobius ova before treatment is considered successful.

The Flagellates

The flagellates parasitic to man are divided into two groups namely the hemoflagellates which live in the blood and lymphatics and the intestinal flagellates and allied forms which live in the intestinal tract or vagina. Giardia lamblia is a member of this latter group.

Giardia lamblia (Giardia intestinalis)

Distribution Giardia is worldwide in its distribution but is particularly common in Egypt. It has a high incidence in children.

Life Cycle The parasite reproduces asexually. Multiplication occurs in the trophozoite form (free motile form) by simple longitudinal fission. Encystment of the trophozoite occurs intermittently and it is the resulting cysts which appear in the stools and not the motile forms. The cysts remain alive in the faeces for ten days during which time incomplete division occurs resulting in the formation of a mature cyst containing four nuclei. Infection occurs by inadvertently swallowing the cysts which on reaching the small intestine release the trophozoites; these little grotesque creatures attach to the small intestinal mucosa by their hollow faces, allowing their flagella to project freely out into the lumen.

Clinical Features Each flagellate fastens itself to the surface of one small intestinal epithelial cell and with the tremendous number of flagellates large areas of epithelium may be covered; in this position the trophozoites appear to feed on the abundant intestinal secretions of amino acids, vitamins and minerals and also to interfere mechanically with the absorption of food, particularly fats and fat-soluble vitamins, from the intestine; this leads to diarrhea (or even steatorrhea) and this in fact was the presenting complaint in two of our five cases. Common to all five cases were the symptoms of abdominal discomfort and weight loss.

Diagnosis The diagnosis is made by demonstrating cysts in the stools. These can be visualized in unstained preparations but are better demonstrated after staining with iodine.

Treatment Atabrine is the drug of choice. Stool examination should be done two weeks after the last dose of Atabrine and if cysts are still present treatment should be repeated.

Concluding Remarks This paper was not written with the intention of covering the entire field of parasitology. Nor was it written with the hope or really even the desire of placing parasitic diseases foremost in the clinician's mind. Instead it was written with the full realization that the most helpful commodity the North American doctor can possess about parasitic diseases clinically speaking is a *high index of suspicion* which can be triggered off by certain typical pictures — the

Ethiopian with vague abdominal complaints; the Mexican with grand mal epilepsy unresponsive to therapy; the Dane with a macrocytic hyperchromic anemia refractory to B_{12}; the farmer from Louisiana with a typical iron deficiency anemia but who with prolonged and adequate therapy fails to improve; the Egyptian with chronic diarrhea. If by reading this paper these 'syndromes' have been imprinted in the reader's mind, the author is well satisfied.

ACKNOWLEDGEMENTS

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Abstract

Bradykinin: J. C. Mitchell. *Arch. of Dermatology,* Vol. 88, No. 1, p. 48, (1963).

Bradykinin is a very potent vasodilator causing stimulation of smooth muscle and increased capillary permeability. Knowledge of the physiological and pathophysiological activities of this substance is as yet poorly understood but the author presents some of the known facts and speculates on the possible production of cutaneous lesions by bradykinin.

It is possible that bradykinin is secreted by the thickened endothelial cells found lining capillaries and venules in the dermis near sweat glands. The reactions producing bradykinin are as folows:

Kallikreinogen (inactive precursor) + activator ➔

Kallikrein (plasma, kinin, forming enzyme) + a_2 plasma globulin ➔

bradykinin (kallidin nonapeptide). Bradykinin is inactivated by peptidase (kininase).

In the corium of the skin of the fingertips, over the scapulae and coccyx and around the joints of the extremities are the glomus bodies composed of an afferent artery, an A-V shunt (Sucquet, Hoyer Canal) and an efferent vein. It has been found that intra-arterial injection of bradykinin produced a digital vascular rexponse identical with reactive hyperemia. It is postulated that the closure of the glomus A-V shunt causes engorgement of the capillary bed and vasodilatation. This explanation is offered for the vasodilation effect of a substance which stimulates smooth muscle.

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Transplantation, Part (I)

J. Seligman
M. Doran
H. Tanzer

This discussion is derived from a recent paper delivered to the A.O.A. Honor Medical Society. It deals primarily with tissue homotransplantation, i.e., transplantation of a tissue from one human to another excluding the case where donor and host are identical twins. In view of the limitation of space, a large and interesting discussion of the immunology involved had to be deleted. The first part of the paper deals with the surgical aspects; the supression of the immune response of host tissues against grafted tissues, which leads to rejection of a graft containing foreign antigens; and the transplantations which have been done and basic methods involved. The second part of the paper deals with some of the broader implications of homotransplantation:— the possibility of the graft rejecting the host, and the prospect of active immune tolerance, i.e. "vaccination" of a neonate in such a manner that he will in future accept foreign grafts.

When animals receive an intrauterine injection of homologous (from the same species, e.g. man to man) cells during their embryonic stage of development, they become tolerant after birth of homotransplants from the same donor. This intraembryonic injection of cells and the subsequent acceptance of transplants from the same donor is referred to as *active immune tolerance* and can only be induced if the cells are brought into contact with the host at time when he is incapable of producing antibodies. This *neutral or adaptive* period was first demonstrated by Burnet* to correspond in most species to the period of intrauterine life; however it may extend in some to the postnatal period e.g. in the rat it extends into the first two weeks of life. In humans the adaptive period is over by eight months gestation.

The demonstration by Burnet that it was possible to induce immune tolerance actively rather than by †passive methods of cytotoxins and x-rays seemed to indicate that the solution to the homograft problem in man was in sight. The advantages of actively induced tolerance over passively induced tolerance were obvious, namely it was lifelong, did not involve expense and long term hospital procedures nor the administration of lethal or near lethal doses of radiation or drugs. However, it was soon to be seen that available methods of inducing such tolerance in animals lead to considerable mortality from a rather curious syndrome. This is discussed in Part II.

The major obstacle to the more widespread use of tissue homotransplantation in humans has been the inability to overcome or circumvent the immune rejection phenomenon. Many approaches to the problem have been extensively investigated; space allows discussion of only a few methods which attempt to induce the recipient to accept the foreign tissues of the donor. These techniques lack specificity in that they are designed to destroy or suppress the RE system as a whole. i.e. they produce *passive immune tolerance.*

Surgical or chemical thymectomy and splenectomy have been carried out with the purpose of destroying the majority of immunologically competent cells; these procedures have had virtually no success in prolonging human homotransplant survival. Saturation of the RE system with colloidal substances such as trypan blue in an attempt to induce functional exhaustion of the RE cells has also been unsuccessful.

The major methods of immune suppression currently of clinical value are irradiation and chemotherapy. Radiation may be administered either locally to the graft or recipient site, or as total body radiation (TBR), the latter given in sublethal doses or lethal doses combined with simultaneous homologous marrow transplantation. TBR is given 12-24 hours prior to transplantation, in doses varying from 150-600 rads. Sublethal doses have been apparently successful in prolonging renal homograft survival between close relatives on five or six occasions; this effect may be more apparent than real, as low doses of TBR are more effective in breaking the immunologic barrier the closer the genetic relationship between donor and host. Lethal doses of TBR create, in effect, a "radiation chimaera", with the many complications of the post-irradiation syndrome, including infection, hemorrhage, and severe gastro-enteritis. The major problem concerns the evaluation of a dose which will on the one hand be sufficient to destroy enough immunologically competent tissue and suppress the rejection phenomenon, and at the same time minimize the post-irradiation complications and prevent the development of homologous or secondary disease.

Cytotoxic and antimetabolic drugs are of prime importance in this field today. The purine analogue

*Burnet Clonal Selection Theory.

†Passive Immune Tolerance:— The production of tolerance (graft acceptance) by depressing the host's immunological system as a whole.

6-mercaptopurine is perhaps the most thoroughly investigated in this regard. To be effective, 6-MP must be administered during the early inductive phase of antibody production. The drug is distinctly limited, however, by its toxicities which include marrow depression, infection, and intrahepatic bile stasis. *Imuran,* the imidazole derivitive of 6-MP, is equally effective and somewhat less toxic than 6-MP, but is somewhat inconsistent in its action.

It is of interest to note that discontinuation of either of these drugs, even after months of therapy and apparent graft acceptance, will result in a typical rejection reaction within one to two weeks. This substantiates the hypothesis that the graft itself is not altered, but remains antigenic even in an apparently tolerant host. In otherwords, immune tolerance implies a central adaptation of the host's lyphoid cells, this adaptation not necessarily being permanent; there is no such adaptation of the transplanted graft, which retains its full antigenicity in the foreign host.

Actinomycin C is a mixture of three antibiotics isolated from Streptomyces chrysomallus; it has a cytostatic action on lymphatic tissue, presumably on the basis of suppression of nucleic acid synthesis. It is particularly useful in combination with other agents, notably Imuran, as the beneficial effects are additive, while the toxicities are not. Other agents such as TEM, methotrexate, cytoxan, and nitrogen mustard have been investigated in this regard, but the doses required are too toxic to be clinically applicable.

Steroid hormones were among the first agents to be tried as immune suppressants; they suppress antibody production by causing a general lymphoid hypoplasia, and delay access of antibodies to the graft by delaying vascularization of the transplanted tissue. Thus, the effects are primarily systemic, though local cortisone is occasionally of some value. The power to suppress the rejection response is confined primarily to cortisone, hydrocortisone, and ACTH. A positive correlation exists between the dosage of cortisone required and the amount of antigenic material in the graft.

It is pertinent at this point to discuss agammaglobulinemia and its relation to the immune rejection phenomenon. Contrary to a widely held belief, it has been demonstrated that some of these patients can and do reject homografts of skin after only slightly prolonged survival. These patients had gamma-globulin levels in the range of 50 mgm.%, and showed no antibody response to standard doses of typhoid or mumps vaccine. It is possible that gamma-globulin is not primarily concerned in transplantation rejection to a significant degree, and that previous successes with homotransplants in these patients may be due to some associated inborn error of protein metabolism not as yet recognized.

Another problem in homotransplantation is the selection of a donor who is most compatible immunologically with the intended recipient. The closer the genetic relationship between donor and host, the greater the chance of prolonged survival; the ultimate example is of course the permanent survival of grafts between identical twins. Mother-offspring grafts survive considerably longer than father-to-offspring, as there is often partial tolerance between the mother and her offspring resulting from an in utero interchange of antigens. Several matching procedures have been investigated in order to determine the donor whose tissues are least foreign to the recipient. Compatability in the ABO and Rh blood groups is desirable, but not always necessary for prolonged survival; minor blood groups seem to be of no significance in this regard. Compatibility with respect to leukocyte antigens, as determined by specific leukagglutination tests is often of more significance than a similarity in red cell antigens. The normal lymphocyte transfer test may prove to be useful as a matching technique. Lymphocytes extracted from recipient R, and injected intradermally into each of a panel of prospective donors will elicit delayed cutaneous inflamatory responses of unequal intensity in each donor, similar to a tuberculin reaction. The intensity of the response correlates well with the survival of a subsequent skin graft from that donor; the weakest reactor provides the longest surviving graft, and hence is the donor of choice. Drawbacks of this test include the danger of spread of infectious disease, and a reaction of a non-immunological character provoked by the injection.

With this background, we may now consider some of the advances which have been made in the field of homotransplantation, and discuss some of their implications. Major organ transplantation is still largely experimental, though notable success has been achieved with renal homotransplants. The rapid, complete, and often prolonged restoration of health following a renal transplant, even to the point of sustaining a pregnancy, has been a strong stimulus to further research in this field. Transplants between identical twins pose no immunological problems, as these are in essence, autografts; of the more than 50 cases recorded, permanent success has been achieved in 90%. The technical skill allowing kidneys to be transplanted was developed as early as 19O5, and the first renal homotransplant was attempted unsuccessfully by a Russian in 1936. To date, there have been almost fifty homo-

transplants carried out, using relatives, indifferent persons, or cadavres as donors.

The selection of the donor is guided by several principles. Close genetic relationship and compatibility in the major blood groups is desirable. Careful screening, including chest X-ray, ECG, urinalysis and culture, BUN, IVP, clearance studies, and renal arteriography are vital in determining the acceptability of the donor. The IVP insures that the patient has two functioning kidneys. Renal arteriography has shown that the left kidney is far more often suitable than the right, partly on account of a long left renal vein. Arteriography demonstrates the presence of multiple renal arteries, which occur in about 20 to 25% of kidneys. The left kidney alone is suitable in 33% of people, whereas the right kidney alone is acceptable in only 3%. Cadaver donors pose additional problems. One must assess acceptability on the basis of the patient's age, mode of death, a stat post-mortem BUN, and urinalysis and culture, the sample being obtained from the bladder via a needle through the abdominal wall. Unacceptable donors include those with infection, abdominal carcinoma, or a history of prolonged shock or nephrotoxic drug intake prior to death.

A major problem in using cadaver kidneys is the uncertainty involved in procuring a suitable kidney; this often necessitates prolonged pre-transplant dialysis of the patient while awaiting someone's untimely death.

A word or two about technique. The left kidney, which is used almost exclusively, is transplanted to the right iliac fossa, anastomosing the renal artery to the internal iliac or hypogastric arteries, and the renal vein to the external iliac vein; the ureter is passed between the mucosal and muscular layers of the bladder, and is sutured to the bladder mucosa. The duration of renal ischaemia is of vital importance; 15 to 30 minutes is often tolerated without any residual damage to the kidneys; one hour of ischaemia is compatible with complete or almost complete functional return; periods longer than 90 minutes are associated with invariable renal shut-down. The period of ischaemia can be prolonged and rendered safer by hypothermia of the donor and the graft, heparinization, and the pre-transplant perfusion of the donor kidney using cooled physiological solutions via a pump — oxygenator and heat exchanger.

Following transplantation, the kidneys undergo periods of anuria ranging from one to three weeks, due to the previous ischaemia. In most instances the graft and host tolerate this well, and diuresis occurs, often to the extent of five to six or more litres per day. Approximately 25 to 40% of function is regained; this is sufficient to lower the BUN and maintain a state of well being. The transplant will reduce hypertension in the host, provided the host's damaged kidneys are removed; the homotransplant will not in itself create hypertension in an normotensive host, unless it is ischaemic.

The majority of grafts are, however, eventually rejected or otherwise doomed to failure. One-fifth of transplants are immediate technical failures. One-fifth of patients die shortly afterwards of infection and uremia, due in no small part to previous radiation and drug therapy. One-fifth of patients are subjected to the classical rejection phenomenon which may occur anywhere from two weeks to one year after transplantation. This is heralded by fever, loin swelling and tenderness, oliguria, a rising BUN, and LDH leukocytosis, hypertension, and a deterioration of general well-being. One of the early signs of impending rejection is the consistent appearance of lymphocytes in the stained urinary sediment. A daily examination of the sediment would allow one to anticipate rejection early enough to reverse the process. Combinations of cortisone, Imuran, and particularly Actinomycin C have been shown to result not only in amelioration of lost function and a fall in BUN, but in actual reversal of hemorrhagic lesions in the kidneys. One-fifth of patients undergo an acute rejection within four to six days of transplantation, and may manifest one or more of five lesions: renal cortical hemorrhage, acute glomerular lesions, cortical necrosis, acute tubular necrosis, or thrombosis of the main renal vessels. This is a humoral, non-cellular rejection characterized by thrombosis, hemorrhage, and a peculiar absence of mononuclear cell invasion. An immune aetiology has been postulated, but is as yet unproven. The remaining one-fifth of patients have enjoyed and still are enjoying good health for periods from six months to almost four years after homotransplantation. Two patients in good health four years after the procedure received their kidneys from their respective non-identical twin.

Two points remain to be mentioned with respect to renal transplants. Prolonged survival in some cases has been attributed to the uremic state in which there is a decreased antibody production and hence a less intense immune response. One must also consider the risk of the graft developing the host's disease; this, however, seems to occur only in transplants between identical twins, and it is reasonable to assume that factors responsible for the original disease produce the disease in the transplant. A lesson to be learned is that the former theory of all-or-none rejection is

no longer valid and that the process may attenuated and even reversed, allowing the patient prolonged periods of active life.

Several attempts at human liver transplantation have been carried out with some encouraging results. Three patients, aged 3, 48 & 67 yrs., suffering respectively from biliary atresia, terminal cirrhosis, and common duct carcinoma, were subjected to transplantation of livers from three donors of comparable age. Two donors were afflicted with brain tumors, the third with massive cerebral hemorrhage. Each recipient had been subjected to a preliminary operation designed to free the liver from its bed, leaving only the vascular pedicles intact. Each was treated with various drugs to suppress the immune response. Two of the recipients were retained in the recovery room to await the imminent death of the prospective donor. As the last two donors were expected to die at any moment, they were investigated fully with regard to liver function, and were monitored on hourly blood pressure and urinary output recordings to ensure that good tissue perfusion was maintained. These donors spent their last hours in the operating room, prepared and draped for femoral cannulations and laparotomy. At the moment of death, the femorals were cannulated, and the body was perfused with 5% dextrose at 15 degrees C. via a glucose primed pump-oxygenator. With the liver thus adequately perfused within five minutes after death, the liver was then dissected and transplanted to the already prepared host with a minimum of Anoxia. The first patient succumbed within four hours from uncontrollable hemorrhage, but the second and third patients survived twenty-two days and seven and a half days respectively. Sufficient liver function was established in both patients to maintain a normal blood sugar level; 150 to 600 cc. of bile were collected daily from a T-tube in the common duct, and 65% of this was conjugated billrubin. In the patient who survived twenty-two days, liver function tests revealed that hepatic function was improving day by day, until death occurred from pulmonary embolism.

A serious problem was the drastic increase in plasma fibrinolytic activity within minutes after establishment of circulation in the graft. This was replaced in a few days by a tendency to hypercoagulability, with increased intravascular clotting. These drastic coagulation defects were both unexpected and uncontrollable, and were not attributable to an acute deficiency of coagulation factors. Despite these difficulties, it is still within the realm of possibility to treat cirrhosis and hepatic carcinoma by liver homotransplantation.

Experimental canine lung homotransplantation has revealed that at least one lobe of one lung must remain intact in the host to permit normal respiratory reflexes and muscular activity. If one lung is removed and immediately retransplanted to the same site, and then the contralateral lung is removed and discarded, the animal will die of pulmonary edema due to the absence of the respiratory reflexes. Interruption of arterial and lymphatic flow also predisposes to pulmonary edema by decreasing the capacity of the pulmonary vascular bed to adjust to changes in blood flow. Lung homografting in man has been attempted as a temporary measure in the management of bilateral aspiration pneumonitis, with the purpose of sustaining life for the period of time required for the pneumonitis to resolve. The graft was then removed before initiation of the rejection phenomena. Widespread implications for lung transplantation include the treatment of emphysema, bronchiectasis, or carcinoma.

Endocrine homotransplants tend to survive more readily in foreign hosts, as the endocrine antigens seem to elicit weak immune responses. Most grafts will survive and function without intact nerve and lymphatic supply; endocrine tissues are often transplanted as minute one milligram fragments in order to insure a large surface area for diffusion of nutrients. Human experience has been limited, variable, and at times, inexplicable. About ten patients with Addison's disease have been treated with fetal or adult adrenal tissue implants; viable tissue has been demonstrated after six months, but viability does not necessarily imply functional integrity. Nevertheless, clinical success has been claimed for up to seven years. Fetal thyroid has improved PBI and radioactive I-131 uptake values in myxedematous patients. Homotransplantation of the thyroid-parathyroid complex has resulted in clinical improvement in hypoparathyroid patients, and has corrected serum calcium levels and the renal tubular control of phosphate. Ovarian homografts in patients with Turner's syndrome have reduced FSH values and have produced estrogen; these grafts function apparently from four to six months. Success with pituitary homotransplants has been claimed in Simmond's disease. On the whole, however, since endocrine deficiencies are partially or wholly correctable by replacement therapy, there is no indication for subjecting the recipient to radiation or chemotherapy for the purpose of transplantation of endocrine organs.

Skin homografts are invaluable as temporary dressings for extensive burns, as burned patients tolerate homologous tissue far more readily than normal persons. Close relatives are the preferred donors, but unrelated cadaver skin has survived for up to twelve to eighteen days in such patients. Fetal membranes -i.e. the amnion and chorion, are excellent biologi-

cal dressings for burns, open wounds, decubitus and varicose ulcers. As these tissues lack specific antigenicity, they survive three and four times longer than skin homografts. Furthermore, fetal membranes are capable of undergoing cellular division and epithelialization. On severe burns, fetal tissue has survived for over a year in some instances.

The successes with organ homotransplantation, though few, have been encouraging. Four patients with kidneys from unrelated donors have now survived over six months; five patients with kidneys from relatives are living more than one year after transplantation, and two patients with kidneys from their respective non-identical twins are alive and well four years after the procedure. A surgeon proposing to remove a healthy kidney from a living donor has a grave moral responsibility, as he must access the risks to the donor as well as those to his patient; the risks of nephrectomy are small but not negligible; one must consider the possibility that the donor's remaining kidney may become diseased. The individual decisions are matters which concern the conscience of the patient, the donor, and particularly the surgeon; for he alone is aware of the factual background from which the likelihood of success can be judged.

Valuable therapeutic measures have often resulted from a purely empirical approach. For example, digitalis and insulin have been used efficaciously for years, yet even now only little is known of their essential actions. It would thus be a tragic mistake to despair of finding a useful method for preventing the homologous tissue rejection phenomenon before the process is fully understood. A prominent leader in the field of transplantation has aptly stated that we now stand on the threshold of a new era of surgery, and have found a new meaning for the old adage, "No man is born for himself alone."

Transplantation, Part (II)

As mentioned above active induction of tolerance in animals often results in a syndrome leading to death. Cells of reticuloendothelial origin injected from a donor to a tolerant host soon find their way into their organ of origin e.g. spleen cells return to the spleen and here multiply and repopulate the organ of the host. Antibody production by these donor lymphocytes may be directed against host antigens. This so called *Graft versus Host Reaction* (G.V.H.R.) was first noted during active immune tolerance induction by Billingham in 1952 when he found that if lymphoid tissue was injected into tolerant mice shortly after birth, within two weeks they stopped growing and deteriorated. For this reason the disease was designated *Runt Disease*. Subsequently it was shown that previous tolerance to donor cells was not necessary and that in fact runting could be produced by inducing active immune tolerance with large quantities of immunologically competent cells (i.c.c.'s). These cells induce tolerance initialy, but subsequently establish themselves as tolerated guests in the corresponding host organs where they multiply and finally begin to produce antibodies against the host organism. Cells originating from spleen, lymph nodes, bone marrow, thymus and blood leukocytes in this order of efficacy can be used to induce runting, the only condition being that the cells must originate from an immunologically competent donor capable of producing antibodies.

It soon became painfully clear that similar G.V.H.R.'s could be anticipated whenever i.c.c.'s from an homologous donor are not rejected by the host. The entire spectrum of disease resulting from G.V.H.R.'s may aptly be termed *Homologous Disease*".

Evidence of the occurrence of homologous disease in man has thus far been lacking and understandably so as it has not yet been possible to produce active immune tolerance in man. It is also understandable that current techniques of production of passive immune tolerance in man have not led to these phenomena since such transplants are usually not retained long enough and since the host is usually capable of rejecting the graft.

One would not expect a syndrome confined to lab animals to cause such a stir. There are several reasons for this interest. The possibility of G.V.H.R. largely explains why recent experimental advances in homografting have not been applied to man. Potential G.V.H.R.'s analogous to secondary disease can be expected to limit the treatment of leukemia and malignancy by heavy doses of radiation and antimitotic drugs in combination with homologous marrow transfusion.

Runt disease is in many ways equivalent to human autoimmune disease in so far as i.c.c.'s regarded by the host as self are able to react against other body components. Autoimmune disease in man is of two basic types. In the first the disturbance is due to alteration of host antigen in which normal tissues are modified or abnormally released into the circulation where they elicit antibody formation. The second possibility, that autoimmunity may imply a change in the antibody forming apparatus would be compatible with *normal tissue* becoming antigenic to an aberrant lymphoid system. The mechanism is unknown but the current theory lies in alteration of host lymphoid cells by spontaneous mutation or as a result of viral infection, chemicals or radiation.

Neoplasms of antibody-forming tissues provide a special case and in fact the *clinical* similarity between lymphomas (Hogkins in particular) and G.V.H.R. in animals has been the subject of concern recently. Both are characterized by multiple infections and poor immune responses; both suffer hemolytic anemia, severe wasting and lymphoid destruction; both demonstrate high titres of autoimmune antibody and both are ameliorated by steroids. Hogkins is associated with marked increase in homograft survival and often shows tremendous lymphoid destruction.

Although the homograft barrier has been penetrated by the production of active immune tolerance in animals it is not without risk and has been considered as yet too hazardous for clinical use due to the possibility of G.V.H.R.'s As technical advances in surgery rapidly increase the field of possible transplants, the one remaining puzzle is, how can one induce permanent active immune tolerance without simultaneously inducing death through G.V.H.R. To add to the problem it has been shown that even *active* immune tolerance is by no means permanent and the most enduring forms of tolerance are induced by just those cells which are most prone to causing runting. Thus testis cells induce neither tolerance nor runting but spleen or lymph node cells induce both tolerance and homologous disease.

Some Implications of Transplantation Immunity and Tolerance in Man.

Attempts to induce homograft tolerance in the human neonate have been largely unsuccessful. The evi-

dence is now conclusive that the human infant at birth has past the adaptive phase as has the fetus at 8 months gestation, and to achieve any effect, interference would have to be much earlier in pregnancy probably at a time when the risks of mechanical interference would be quite high. Furthermore because of the hazard of G.V.H.R. the innoculum would have to consist of noncellular antigenic extracts or else cells lacking immunologic competence and there is no certainty of their efficacy. A more attractive alternative is the presentation of antigen to the fetus by *maternal* transmission. Experiments to modify placental permeability by hyaluroridase or irradiation of the uterine norn in pregnant animals have produced some degree of tolerance to maternal homografts. The possibility of spontaneous induction of tolerance by transmission of maternal cells to the fetus has also been the subject of enquiry.

Tolerance to only one individual's tissues, even though it be the mother, would in practice impose severe restrictions on the surgical exploitation of homograft tolerance. A means of creating "universal recipients" is necessary. The sharing of transplantation antigens between members of outbred populations suggests that the total number of transplantation antigens is quite finite though the permutations responsible for individual compatibility are quite numerous. By pooling antigens from several different sources one might embrace the entire spectrum of transplantation antigens demanded for induction of complete homograft tolerance. Recent experiments have succeeded in inducing *polyvalent* type of tolerance by means of pooled antigens from multiple donors.

Far more susceptible than homograft tolerance in man is the possibility of inducing immunologic tolerance to blood group antigens. The prize to be won is primarily the elimination of erythroblastosis by induction of tolerance to A, B, and Rh antigens. Several paths are currently being investigated.

It is now accepted that no one is born with A and B isoantibodies but rather their production begins at three to six months of life as a result of acquired immunity to these ubiquitous antigens probably through their ingestion in food or inhalation. If these antigens could be presented early enough tolerance could be induced. Although the human infant has passed the adaptive period for homotransplantation antigens at birth, this does not mean that he has passed the adaptive period for red cell antigens as well.

A very basic question arises at this point. The fetus is in fact a vascularized homograft in the mother. Why does it survive so long? It is well known that entire cells of fetal trophoblast are continually being shed into the maternal circulation where they have been demonstrated from the eighteenth week until ten months. The cells of syncytial trophoblast may turn out to be not fully antigenic in the transplantation sense but provide a non-antigenic buffer between mother and fetus.

If however the trophoblast is fully antigenic, then one intriguing possibility is that the continual release of antigen into the maternal blood stream may desensitize and paralyze the maternal immune response. One may also speculate as to whether transplantation immunity ever causes sporadic or habitual abortion. To date this has never been demonstrated.

Finally, I should like to mention a problem arising from the possible penetration of the homotransplantation barrier in man i.e. the problem of senescence or aging. Aging and natural death have been postulated to result from an accumulation of chromosomal damage in somatic cells. As an individual grows older body cells mutate and it has been shown that titres of autoantibody to *"normal"* tissues increase with age. Death occurs when the amount of genic damage reaches a lethal bound.

It is diminishing to consider our present state of helplessness in the face of the major limitation of life; the inevitable accident that sooner or later introduces a flaw in the copying of a genetic pattern. If this theory is right, the specific type of degeneration which leads to natural death in any given person will be dependent upon the nature of the genetic weaknesses with which he starts life. Every individual is born with a certain degree of immune tolerance to his own tissues and though somatic mutation is inevitable, its effect is likely to be more marked in an individual already carrying a single dose of a lethal or harmful allele that is significant for the tissue concerned.

Methods of transplanting tissues between adult animals, as well as the possibilities of culturing organs and tissues in vitro for ultimate substitution in senescent animals, would conceivably enable individuals to live far beyond the present maximum recorded age of 118 years. It is interesting to conceive of a 200 year old, who may have received a replacement transfusion at birth only to be followed in later life by replacement of each of his major organ systems — except of course his seat of reason, for which even technical difficulties are insurmountable. Such a strange concoction of a youthfully rejuvinated body and senescent mind may well become the rule rather than the exception in future years. The possibility of prolongation of life by organ and tissue homotransplantation seems to toy with the whole order of living Nature.

Abstracts

Arch. of Int. Med., Jan. 1964, p. 122.

Clubbed Digits: An Enigma, J. O. Just-Viera

Clubbing or pulmonary hypertrophic osteoarthropathy is a common sign which is often misdiagnosed. The pathogenesis of this process is unknown but changes eventually occur in the soft tissues, bones, periosteum and the joint itself. It is due to a variety of causes and in this article the author presents four case histories in illustration of some of the causes.

A common denominator of the various causes of clubbing has not yet been found. At the present the two most favored theories on the basic cause of clubbing are peripheral blood flow in excess of physiological requirements due to either vascular fistulas or an autonomic vascular reflex or a physical alteration in the blood causing anoxia.

Arch. of Dis. in Childhood, Aug. 1963, p. 343.

The Relation of Edema to Serum Protein and Pseudocholinesterase Levels in the Malnourished Infant

In this article the authors investigate the possibility that hypoproteinemia is one of the factors causing fluid retention in Kwashiorkor. The assessment of degree of edema was based on clinical observation and weight loss after treatment. Serum protein determinations were done simultaneously.

From their results the authors conclude that the osomotic effect of reduced serum protein levels may perpetuate the edema of more severe malnutrition but it is not the only precipitating factor. Indeed, the hypoproteinemia may be merely dilutional. Cases with severe edema had low serum proteins but the converse was true in only 50% of the cases.

Liver enlargement and low pseudocholinesterase levels correlate significantly with severe edema. Extreme fatty accumulation in the liver may contribute to edema and/or hypoproteinemia.

Neurology, Dec. 1963, p. 1054,

Methyl Bromide poisoning with Nervous System Manifestations Resembling Polyneuropathy, A. D. Katarjian, A. S. Shaheen

This paper represents the study of an incident of the industrial poisoning of eight men, ranging in age from 19 to 43 years, by methyl bromide. In contrast to some earlier reported cases, the manifestations of the poisoning were neurological and resembled those of a polyneuropathy. The earliest symptom was paresthesiae, followed by sensory deficits and paresis in the distal parts of the extremities. Heaviness in the legs, unsteady gait and various sensory and motor signs developed.

In hospital the patients were divided into two groups: one received vitamins B1, B complex and physiotherapy; the other received only physiotherapy. Both groups recovered fully in six to eight months.

Vogt, Kayanagi, Harada Syndrome: W. C. Johnson. *Arch. of Dermatology,* Vol. 88, No. 2, p. 146, (1963).

The syndrome consist of meningeal irritation, nontraumatic uveitis, poliosis, vitiligo, alopecia, dysacoucia. The author describes a case seen by him. He discusses the cutaneous manifestations which are, in order of decreasing frequency, poliosis, vetiligo and alopecia (usually alopecia areata). These manifestations usually occur after ocular disease is present so there is a tendency for the disease to be diagnosed late. This is unfortunate for early treatment reduces ocular morbidity.

Because the etiology is unknown and the clinical course variable, treatment is difficult but steroids, mydriatics and acetazolamide seem to help.

The Effect of Drugs on Teratogenesis

F. W. Furlong

"..... curtail'd of this fair proportion,
Cheated of feature by dissembling nature,
Deform'd, unfinish'd, sent before my time
Into this breathing world, scarce half made up."

King Richard III (Act I, i).

Introduction: The Scope of Teratogenesis and the Place of Drugs.

Many centuries ago Pliny wrote, "Nature creates monsters for the purpose of astonishing us and amusing herself." This was an early animistic attempt to explain a still fascinating and little understood problem — the problem of teratogenesis (Greek: teras, monster; genesis, origin). The ancients attributed malformed human foetuses to intercourse during the menstrual period, and held that the god Vulcan of Roman mythology and the fabled Greek centaurs were products of the violation of this taboo. In 1890 one could read in a medical textbook that, "Impressions made upon a pregnant woman are capable of causing mental and bodily defects in her child." This theory of "maternal influence" still holds sway with large numbers of the public; thus a mother who is frightened in the sixth month of her pregnancy by a man with a "cauliflower ear" may expect to find her child born afflicted with a defect of the ear, or in some other fashion symbolic of the incident.

In this century medical science has implicated a whole spectrum of predisposing factors and causes of teratogenesis. Certain malformations are inherited with a regularity and a predictability which leaves little doubt of their genetic origin. Some are of dominant inheritance; some are recessive in nature; many other malformations suggest heredity as the causal agent, but in a manner much less easy to follow. At the other end of the spectrum are malformations which clearly stem from an altered environment.

This paper received the Charles E. Frosst Scholarship in Medicine ($500) "awarded to the final year medical student, who having placed among the first 25 in the previous 3 years, submits the best essay on a prescribed subject chosen by the Company".

Between these poles lies a foggy mystery land consisting of many gross malformations whose causes are not well understood. It is in these last two areas that our attention has been recently centered by the alleged production of human foetal abnormalities attributable to the use of the drug thalidomide by the mother in the early weeks of pregnancy.

Terminology

Translating the Greek roots literally, the word teratogenesis means the origin or production of monstrosities. However this term is frequently used in a more comprehensive sense to include the production of any anatomical abnormality in the course of intrauterine development. This application is very convenient, for it has been found that certain drugs, for example thalidomide, while sometimes producing true monstrosities, at other times produce defects of a less sensational nature (such as anal stenosis or malformed auricle). Certain terms are applied to specific monstrosities. Should the posterior appendage buds of an embryo fuse to form a fish-like tapering caudal half to the body the condition is termed "sirenomelus" (siren or mermaid). When there is complete failure of both pairs of limbs to develop the condition is called "amelia". When hands and feet appear directly attached to the trunk the abnormality is "phocomelia" because of the resemblance of the malformed limbs to the flippers of a seal.

The materials which have been explored as possible teratogens include much more than the term "drugs" conveys to the general public. Not all teratogens come in bottles with labels on the outside. Thus we must consider not only such obvious "drugs" as certain antibiotics and sedatives, but also excess carbon dioxide or oxygen, hypervitaminosis, and various antimetabolites. The lack of certain chemicals in the embryo's developmental environment should also be our concern; thus defects in the maternal diet, hypovitaminosis, and hypoxia should be surveyed.

Sources of Knowledge: a preliminary evaluation

Unlike Pliny we must have more information than can be supplied by speculation on nature's motive in producing monsters. Our source of knowledge is essentially two-fold: human clinical material and experiments performed on laboratory animals.

The defects in the former as a strictly scientific device are at once apparent. Poor memories, incomplete records, inclusion of teratogens in some non-prescription drugs, and failure to report all congenital malformations reduce the information we could derive from these misfortunes. It has been suggested that had thalidomide produced only a minor abnormality such as anal stenosis rather than the more spectacular gross deformities which it did, it might well have gone undetected much longer. Whatever the defects of this source may be, it is a necessary one, for it is an established fact that there are some marked differences between the production of human and animal malformations. Therefore while effects on foetal mice may warn us of possible effects on humans, the absence of teratogenic effect on laboratory animals does not rule out the possibility of adverse results with humans. Moreover while certain observations in animals may in the future help solve the riddle of the mechanism of action of teratogens we cannot conclude from such experiments that an identical mechanism is at work in humans, for not only are there great species differences but we now know that foetal metabolism differs strikingly in certain ways from adult human metabolism. Thus there are certain defects inherent in both methods no matter how carefully they may be used and how conscientiously reported.

The experiments are of two major types. A pregnant female animal may be administered, orally or parenterally, a suspected teratogen of known dose, on a given day after conception for a known duration under conditions as standard as possible. The foetus is sometimes allowed to develop to term, but often is removed at a certain date in order to study the deformities as they progress and hence attempt to determine something of the mechanics involved. In the second class of experiment a lower form of animal is used (for example the Medeka fish) and the immediate environment of the embryo as it develops is altered chemically, ionically, or in some other known way, on a known day post-conception under standard conditions. When forms differing more greatly from man are used, the problems of interpretation are, of course, accentuated.

Popular experimental animals are mice, rats, and rabbits. Mice seem to be the animal of choice in most experiments on drug-induced tertogenesis. There seem to be several good reasons for this. Mice are among the most sensitive of animals in the production of abnormalities with drugs (thalidomide is an exception to this rule); conception is easy to detect, and they are financially less of a burden than rabbits and other animals. (Monkeys would be ideal, some authorities feel, but the cost is much greater than that of mice or rats). While much has been said of the weakness of the experimental approach to this problem it must be mentioned that it possesses certain obvious advantages. The various parameters can be juggled at will, controls are available, and the time involved in gestation is less than in humans. Moreover in animals, especially mice, we can produce a homozygous line; this is of great importance as the genetic background has been found to alter the effect of the drug greatly. In the human race we have an exceedingly heterozygous population and accordingly we find that the effect of a drug varies greatly.

The Results of Experimentation — Some Major Principles

First we will outline certain broad principles which have been determined from animal experiments. Next we will see what state of affairs exists in human teratogenesis and how well these principles fit the human pattern. Lastly we shall return to the results of experimental work in more detail, and to a consideration of possible mechanisms of action.

In both human and animal studies it is found that the foetus is sensitive to teratogens only during a limited period in early pregnancy. Once this critical period is passed teratogens administered to the mother will not produce structural abnormalities. There is within this critical period a shorter period of special vulnerability for each structure in the developing body when it is exceptionally sensitive. This time varies from structure to structure, and is believed by some authorities to coincide with the period of greatest mitotic activity. (The time of administration of a teratogen may be deceiving; for example it may take many days for the necessary concentration to build up so that the time of administration need not be the same as the time at which the agent exerts its harmful effect.) This time specificity, as it has been called, was demonstrated by Nelson in 1952 by administering folic acid antagonists to pregnant female rats:

Day after fertilization on which drug was administered	result in foetus
1-9	resorption
11-12	skeletal abnormalities
13-15	mesodermal deficiences (respiratory and renal systems)
15 days or more	normal offspring delivered.

It is found that malformations are not produced in organs which are fully developed at the time the teratogen is administered. The critical period may be the time when organogenesis is proceeding most rapidly or may be prior to this, perhaps even before there is a visible primordium. However the critical period for an organ is different for different teratogens. This leads us to suspect that there is no one blanket explanation for how all teratogens act, and that there is probably no one focus in some biochemical pathway at which they all (or even one, at all times) exert their deleterious effect.

At times the results are found to be non-specific: i.e. one teratogen may produce a variety of defects depending on the time, dose, duration, and genetic background, and sometimes different teratogens may produce the same defect. However, at times some agents do tend to produce an array of similar defects in different strains and species (mice and rats). Under conditions of maternal vitamin A deficiency we can predict a high incidence of defects of the eye and urogenital system among the offspring; in riboflavin deficiency mice and rats of various strains are born with frequent defects of the long bones and axial skeleton. Folic acid deficiency affects almost all systems in equal incidence.

The susceptibility of the embryo varies with the genetic background of the mother and foetus. Cortisone administered during early pregnancy will produce cleft palate in the mouse and rabbit, but fails to do so in the rat. The strain of animal within the species also has a marked influence on the frequency with which any teratogen induces malformations. Cortisone will induce teratogenesis in four to one hundred per cent of mice depending on the genotype of the strain studied. The genetic differences apply to specific organs as well: thus in one strain of mouse a maternal riboflavin deficiency produces a high frequency of cleft palate and a low frequency of limb defects while in another strain the reverse situation obtains. It is just this genetic influence which makes us unable to say that a drug which failed to produce malformations in animals will not produce malformations in humans.

The dose of the teratogen is also a major factor. Many drugs, harmless in therapeutic concentrations are teratogenic when given in excessive quantities; e.g. when hypervitaminosis A is induced in the mother. However salicylates and some antibiotics are teratogenic in experimental animals under certain conditions at doses comparable on a percentage-body-weight basis to those used therapeutically in man. In animals it is found that there must be a noxious but not too harmful stimulus applied to the developing embryo; i.e. there is a relatively narrow range of dosage which can produce deformed young. Should the dose fall below this range the young are born alive and normal. Should the dose fall above this range the young die in utero. It has been shown that agents which cause malformations will usually kill the embryo when used at higher doses. While some agents which cause the death of the embryo in utero are non-teratogenic at lower doses, it is a generally established principle that any drug which will kill the foetus at a high concentration will deform it if given in a lower dose. Woolam has concluded from this that if the dose needed to kill the foetus is close to that which would kill the mother then there is little danger of producing malformations, and the greater is the difference between the lethal dose for the embryo and that for the mother then the greater is the probability that the drug will produce congenital malformations. This depends then on the little understood differences in the metabolism of adult and embryonic tissues. Obviously drugs which are quickly fatal to the mother are not a problem here. The ratio of teratogenic dose in animals to therapeutic dose in man on a percentage-of-body-weight basis varies greatly with the drug and with the species. The dose of cortisone required to produce cleft palate in the mouse is four hundred times the therapeutic dose in man. For cortisone in the rabbit the ratio is twenty to one, and for tetracycline in the the rat it is one to one.

The frequency and type of malformation produced by a given teratogen are also found to vary with a host of other environmental factors such as maternal weight, the position of the embryo in the uterus, maternal age and reproductive history. One striking result is that only some members of a litter in which the strain is sufficiently homozygous to preclude, it is thought, any significant genetic differences, are found to be deformed, and as well shall see, the position in the uterus is an unexplained factor. The effect of certain teratogens may be modified by simultaneous administration of other substances. Thus two teratogens used at doses at which each alone would be incapable of producing

malformations may cause a high frequency of congenital abnormalities when given simultaneously. Some researchers have found that the teratogenic action of Vitamin A excess may be enhanced by cortisone and alleviated by thyroxine. Remembering then that the probability of producing a malformation with a given agent, and the type of malformation produced depends on the developmental stage of the embryo, the dose of the drug, the species, the genetic constitution of mother and embryo, and a host of other factors, let us turn to the field of human drug-induced teratogenesis and determine what can be added to our knowledge.

Human Drug-induced Teratogenesis

Towards the close of 1961 and in early 1962 there began to occur reports of a correlation between a previously rare limb anomoly, phocomelia or seal-limbs and the consumption by the mother during the first three months of a new drug called thalidomide.

Trade Names:

Contergan (West Germany)

Distaval (British Commonwealth, excluding Canada)

Softenon (Portugal)

Talimol (Canada)

Kevadon (U.S.A. — not released).

Many other drugs contained thalidomide: Algosedive, Grippex, Peracon-Expectorans, Polygripan, Asmaval, Tensival, Valgis, Valgraine.

To be an effective human teratogen, a drug must be administered during the first three months of pregnancy, that is, during the period of embryonic differentiation. It is for this reason that thalidomide has been so effective, for it was sold as a sedative and antiemetic for morning sickness, and morning sickness is most troublesome at that very time in early pregnancy when the embryo is most in danger. Preparations containing small amounts of thalidomide were also sold as tranquillizers since the drug was considered safe — an overdose produces a sound sleep but never fatal poisoning. Thalidomide has, however, been found to cause glossitis and polyneuritis in the adult suggesting that its peculiar danger lies in the fact that it is only slightly toxic to the adult while exerting a definitely harmful effect on the developing embryonic tissues. As in animal experiments it is the difference between the toxicity to the adult and to the embryo as it develops which is of major importance. Possibly morning sickness is associated with hormonal and nutritional disturbances in the mother which render the offspring more susceptible to the effects of the teratogen.

Polyneuritis occurs after two to twenty months of use and like the teratogenic effect there appears to be little correlation with the dose and duration, and the upper limbs are affected more than the lower. The changes were predominantly sensory and of a "glove and stocking" distribution. Several authors have mentioned a predominance of women developing polyneuritis but it is difficult to determine whether women are more susceptible (which fact would bear on the teratogenic effect) or have merely ingested more thalidomide.

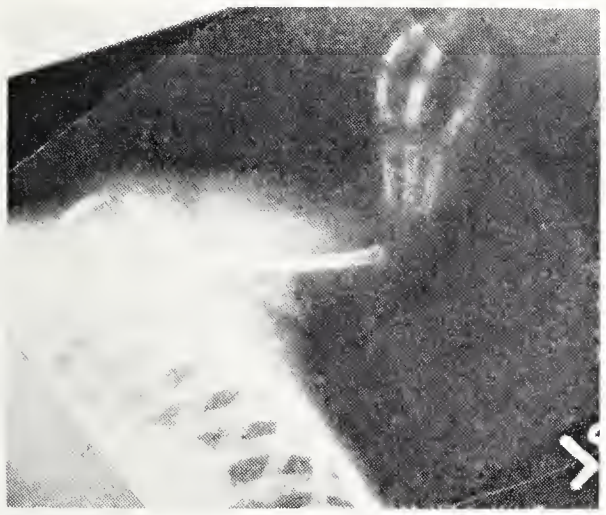
The most frequent abnormality associated with maternal use of thalidomide is a varying degree of micromelia. This is usually bilateral although seldom completely symmetrical. As with the neuropathies, the arms are affected more than the legs. (The figures vary with the authority but generally fifty per cent of cases have deformed arms alone, twenty-five per cent deformed arms and legs, and three per cent just deformed legs). The long bones are primarily affected; there may be a normal or abnormal number of segments in the distorted limb but usually there is at least a rudimentary elbow joint. Short phocomelic appendages without any intermediate segment or amelia with just rudimentary fingers at the shoulder girdle are less frequent. Radiologically the radius may be absent, the ulna and humerus absent or shortened and the attached hands and fingers may be deformed. Often a short stump of arm bears a hand with two fused digits on it. In the shortened leg, the tibia is most commonly absent.

A central hemangioma extending from the forehead over the nose to form a moustache on the upper lip is considered by some authors as characteristic of the syndrome, and has been reported in some series in as much as two thirds of the cases.

A common pattern: phocomelia of both upper extremities and a midline hemangioma on the forehead.

The mother had used thalidomide in the second and third months of pregnaney.

The left arm consisted of a small remnant of the humerus, a shortened ulna and three digital rays. The right had a shortened ulna, three digital rays and a hypoplastic second digit. Both wrists had a fixed radial flexion deformity. The radii and first digits were missing bilaterally. (Mellin, Katzenstein, New England Journal of Medicine, 1184, Dec. 6, 1962.)



X-ray of the left arm of the same case.

Associated with the limb deformities in severe cases and sometimes occurring as isolated lesions are various other malformations such as hypoplastic, enlarged or deformed external ear, and malrotations, stenosis and atresia of the gastrointestinal tract. Duodenum and oesophagus appear to be favoured sights for gastrointestinal anomalies but the anus has also been affected. Other lesions reported are asplenia, absence of appendix and gall bladder, choanal atresia, abnormal uterine musculature, small eyes or eyes completely replaced with fibro-fatty tissue, and a wide variety of genito-urinary and cardiac lesions. (The evidence of a connection between the less common lesions and thalidomide is not as substantial as in the case of the limb defects).

Atretic Auditory Canal and Hypoplastic Ear Lobe.

Such anomalies have been reported following maternal thalidomide ingestion. In this case the mother denied taking any sleeping or tranquillizing drugs.

The sex distribution is equal, and although there is a higher than average mortality, the survivors appear to possess normal intelligence. Abnormalities of the bones of the skull or spine are not usually found.

According to Taussig the critical period for thalidomide's teratogenic action is between the thirtieth and fiftieth day after the last menstrual period. (Others estimate it to be between the twenty-eighth and forty-second day inclusive after conception.) Many women who have taken the drug during pregnancy but after the sensitive period are known to have given birth to normal children. As little as a single dose of 125 mg. has been followed by delivery of a phocomelic infant, whereas in a few instances (Taussig, Mellin, Katzenstein) women are known to have taken thalidomide during the sensitive period in much greater doses and yet given birth to a normal infant. How many other cases of this have occurred is open to speculation. At times one dose causes a severe malformation, and repeated doses, only a minor malformation. Moreover thirty cases of phocomelia have been reported in Liverpool and not all can be attributed to thalidomide. Considering these facts, it is not justified completely to reach the oversimplified conclusion (which one might extract from popular newspapers and magazines) that the relationship is always a simple clear cut cause and effect one. Obviously many modifying circumstances are in operation here; moreover, thalidomide may not alone be responsible for the increased incidence of these deformities, nevertheless, the incidence among women who have taken this drug, and the appearance of hitherto rare anomalies are sufficiently great for us to state with some confidence that some causal relationship does exist. Two cases in West Germany have been reported, where Contergan taken in the first pregnancy resulted in a malformed child, but a second pregnancy without the drug terminated in the birth of a normal infant. Between two and three thousand affected babies have been born in West Germany between 1959 and the beginning of 1962. Lenz estimates the incidence of phocomelia following thalidomide administration to the mother in early pregnancy as twenty per cent, but others (Jones, Williamson, Burley) report a lower frequency.

Although, as we shall see, these abnormalities have been duplicated in experimental animals, using thalidomide, the mechanism of action of thalidomide is still unknown. (February 1963.) However, certain known facts from human embryology may help to clarify our thinking about these malformations. The development of the limbs begins in the fourth week with the appearance of the limb buds. The anal membrane is formed when the cloacal membrane is divided in the seven-week embryo by the anorectal septum which grows down to divide the hind gut from the urogenital sinus. The membrane then proliferates to form the anal plug which grows inward; during the eighth and ninth weeks it becomes canalized to form the anus. The pinna of the external ear also achieves its final form between the eighth and tenth weeks by fusion of the primary tubercles. It is apparent that an agent applied after the limbs had differentiated could affect the ears and anus and not the limbs, whereas when the teratogens were applied earlier only the limbs would suffer. Indeed we do find cases where the anus

and ears are affected and the limbs have developed normally. There is undoubtedly much overlap and variation in the time and rate of differentiation of the organs in different embryos.

The status of other teratogens is less well established. Cortisone is not proven beyond doubt to be a human teratogen. Cortisone given to animals in early pregnancy can produce cleft palate. In man the results are reported to be less predictable. According to Black, from two hundred and sixty pregnant women given pharmacological doses of cortisone or its derivatives during the early months of pregnancy there resulted eight stillbirths, one abortion, fifteen premature infants, two full term children with cleft palates, and one transient adrenocortical failure. It has been pointed out moreover, that cleft palate, not associated with harelip, is rare when cortisone is not involved, but when cortisone is involved in the maternal history in the early months, there is an increased percentage of cleft palates without associated harelip. A similar situation holds for anal stenosis and thalidomide. When thalidomide has not been consumed the anal stenos is predominantly of the "high" type, and the incidence of the low type is less than 0.9% of the total anal stenoses, but when thalidomide is involved the percentage of the low variety rises. With the present evidence it might be well to avoid large doses of cortisone in the first trimester.

There is no evidence that corticotropin has any direct effect on the foetus, as it does not appear to cross the placenta; however, the secondary rise in maternal steroids may have the same effect as cortisone administration. In animals, congenital malformations have been produced by maternal hypovitaminosis and anti-vitamins. In humans there are a few recorded cases of hare-lip, cleft palate, hydrocephalus, and meningomyelocele following the use of aminopterin in a futile attempt to induce an abortion. Other agents used for their anti-leukemic properties (aminopterin, Busulfan) are suspected for similar reasons. Bemegride and glutethimide whose formulae resemble that of thalidomide, have not been shown to be teratogenic to humans. Sedation with barbiturates is probably the safest course to follow at present, in the early months of pregnancy.

Black reports cases of masculinization of female foetuses following the use of certain hormones in the first twelve weeks of pregnancy. The anatomical masculinization is akin to that found in the adrenogenical syndrome, and often buccal smears are necessary to confirm the true (chromosomal) sex. Three groups of hormones are incriminated: androgenic compounds (testosterone, methyltestosterone), progesterone and its analogues, and a synthetic estrogen, stilboestrol. This is not to be confused with the masculinization that androgens may produce in the foetus after three months (an enlarged clitoris and swelling of the labia at birth) which are reversible within twenty months after delivery. Anabolic steroids such as norethandrolone may also be incriminated. Uhlig (1959) reported malformations following the use of large doses of estrogens. It is perhaps wise at present to use hormone preparations, especially those containing androgenic or estrogenic activity, only when we have carefully weighed the hoped for gain against the possible harm which may be done.

Thus, we find in human material a great deal of variation; however, there are clear cut indications that at least some agents have a teratogenic action; it seems highly probable that the great variation observed in human material is due to factors already outlined under experimental work; genetic background may perhaps render some women immune to the action of thalidomide. Differences in maternal nutrion, certain anti-teratogenic agents, infections, hormonal upsets, even psychogenic factors (which can produce hormonal changes) are variables which we cannot control here, and which may play a large part in determining the probability and type of malformations produced. Much remains undiscovered! Does an excess of vitamin A in the mother produce monsters as it does in rats? Perhaps we shall never know unless some day, a pregnant women develops an insatiable desire for polar bear livers. Let us return then to the experimental field, the principles of which have guided us in appraising the results of thalidomide and other agents, and look at some of the experiments closely and critically, attempting to discern a mechanism of action.

Experimental Results—Possible Mechanisms of Action

Virtually all defects produced in man can be produced in experimental animals. The agents which have produced malformations in the young, when administered to the mother early in pregnancy are legion:

I. Maternal deficiency of: vitamin A, riboflavin, pantothenic acid, folic acid, vitamins D and E.

II. Vitamin antagonists: galactoflavin, X-methyl folic acid, Aminopterin, X-methyl pantothenic acid, 6 aminonicotamide, Thiadazole.

III. Vitamin excess: Vitamin A.

IV. Aminoacid antagonists: azaserine; nucleic acid antagonists: 2, 6 diaminopurine, 6 chlorpurine thioguanine, 5 fluorodeoxyuridine, 6 mercaptopurine.

V. Alkylating agents: Chlorambucil, Busalfan, Nitrogen mustard.

VI. Antibiotics — Tetracycline, Penicillin and Streptomycin, Actinomycin.

VII. Caffein, salicylates, nicotine, thalidomine, aminopterin, trypan blue, adrenalin, insulin, posterior pituitary extract.

This by no means exhausts the list.

Shortly after the data on human material had become impressive Somers (Lancet, April, 1962) succeeded in producing deformities in rabbits similar to those seen in humans. The pregnant female rabbits (in the weight range of 3.3 to 3.5 kg.) were given .5 grams (150 mg/Kg. weight) of thalidomide orally on each day from day eight to day sixteen of pregnancy. The results were as follows:

Rabbit	born,	stillborn,	deformed
1	8	2	7
2 thalidomide	6	2	4
3	4	1	2
4	0	0	0
5	3	0	0
6 control	9	0	0
7	8	0	0
8	9	0	0

Three rabbits treated with thalidomide bore stillbirths and young with deformities. The fourth rabbit was overdue and was sacrificed; the uterus was overdistended with straw coloured fluid indicating that the embryo had died and autolysis had occurred. In the first litter seven of the young showed limb defects in the front and rear legs. The front legs were shortened due to a reduction in the radius and ulna, while the rear legs showed a variety of deformities. As in other experiments unaccountable differences between litter mates was observed.

The importance of genetics in determing how a teratogen acts is shown in the following experiment on two different strains of mice. Under standardized conditions, two homozygous strains of mice (strain A and strain C57BL) were treated with cortisone acetate, 25 mg/day, for four days, starting on the eleventh day of conception. The results were as follows:

Mother	Father	% cleft palate in the offspring.
A	A	100
C57BL	C57BL	19
A	C57BL	43
C57BL	A	4

It seems that we are dealing with two strains, one genetically sensitive and one relatively insensitive to the teratogenic effects of cortisone. When we cross these strains so that the mother is of the sensitive strain we find an intermediate number of cleft palates in the offspring. This is what we would expect if the malformation sensitivity depended solely on the genetic background of the foetus. However when the father is of the sensitive strain, and the mother is of the non-sensitive strain, the percentage of foetal defects is surprisingly less than when both parents belong to non-sensitive strains. Since these are virtually homozygous strains we can conclude that the effect which the teratogen exhibits, depends on the genetic background of both mother and embryo.

Type A shows a spontaneous predisposition to cleft palate; type C57BL does not. We know that cleft palate occurs if the two shelves forming the palate fail to fuse. These shelves grow in from the right and left sides above the tongue. Factors which alter fusion are growth rate and alignment (which necessitates some rotation of the shelves to complete fusion), and the proximity of the shelf bases which in turn depends on the head width, and size and pressure of the tongue. The shelf alignment seems to be the most critical factor in spontaneous cleft palate. In type A the shelves grow and align more slowly than in type C57BL. Cortisone is found to slow shelf growth in both strains. By the time the shelves are ready for fusion in type A, the head is so wide that the shelves must remain apart. In C57BL however, in spite of retardation, the processes fuse before the head reaches the critical width at which fusion becomes impossible. This experiment shows, as others have shown, that only some of a litter are born defective. Since these strains are inbred, the genetic background is the same, and other factors are kept as constant as possible, therefore we might expect all litter-mates to be equally afflicted. In this experiment embryos occupying the sites nearer the ovary showed the defect more frequently than those more remote from the ovary. This was the case with both spontaneously occurring and cortisone-induced cleft palate. The blood supply to both parts of the uterus is the same; the explanation remains obscure.

At present it is impossible to say with certainty how thalidomide or cortisone act in inducing abnormalities. There has been speculation that they enter the cell and act as enzymatic inhibitors at various points in biochemical pathways. Some have suggested that there is interference with glutamic acid or vitamin B metabolism, while Dr. Kalow relates that recent work has suggested that thalidomide may have some effect on pyridoxine. We must remember that our difficulty is com-

pounded by the undeniable fact that adult, infant, and embryonic metabolism differ greatly, and many substances are handled in different ways in the three groups.

If the drug does enter the cell and interfere with some unknown biochemical pathway, then we may surmise that each teratogen produces developmental errors by specific pharmacological actions on particular embryonic tissues at a particular time. Thus each agent would produce an array of defects, depending on what metabolic pathways it interfered with at a given stage of development. Little, too, is known about the specific results of the metabolic disruption wrought by the drug on the developing systems, which may range from death of certain groups of cells at important stages, to mitotic aberrations, altered inductive relationships and misplaced cellular migration.

A simplified concept of great importance has long been put forward by Stockard as a result of his classic experiments with the marine minnow Fundulus. He noticed that various agents applied at the same phase of development tended to produce the same range of defects, and that the common property of the disturbing agents was the power of stopping or slowing growth. Any agent, chemical or physical, would exert this retarding action, he said, most strongly on whatever developmental processes was occurring most rapidly at the moment when the agent was applied. For example, when the nervous system is being transformed from a thickened axial plate into an internally placed tube (the most rapid differentiation) a disturbance would produce a defect of the nervous system, while other organ systems growing more slowly would be unaffected. The inhibiting action would not have to last long, for the center of accelerated activity shifts from one organ to another as development progresses, and if an organ failed to differentiate properly at the time of its transient metabolic dominance it would never fully compensate for this loss. However this concept may help us to explain some abnormal conditions, the malformations which have appeared seem to be more varied than can possibly be accounted for on the basis of a mere cessation or retardation somewhere along the course of normal development. There is probably some more specific action of various teratogens — some chemical reason why it picks a certain organ as its "target", and a variety of aberrations which it may produce in the target. The truth may well combine the several concepts.

We have supposed that the agent enters the cell and interferes with the metabolism. Some thought must now be given to the possibility that the teratogen may act on the cell surface changing the turnover of metabolically important ions. It has long been known that changes in concentration of substances normally present in sea water causes anomalies in different fish embryos.

Smithberg has, I believe, shown that this possibility must be considered. He found that tolbutamide sodium introduced into the medium of the developing fish, Oryzias Latipes, caused certain abnormalities:

1. Abnormal intraembryonic and extraembryonic circulations associated with heart anomalies.
2. Degeneration of the derivatives of the eye cup (the lens was intact).
3. Abnormal curvature of the trunk and tail.

Four stages of embryo were used from the two cell stage to the twenty-four hour stage; four concentrations of the drug and four exposure periods (one to four days) were used. Each of the three factors asserted its effect independently. The earlier the form treated, the higher the concentration used, and the longer the treatment period the greater was the likelihood of a defect being produced. Every abnormal embryo showed stasis or absence of intraembryonic and extraembryonic circulations, and associated heart defects.

The addition of glucose alone to the medium did not prove teratogenic; however when glucose and tolbutamide (above a certain concentration) were used, the percentage and severity of the anomalies were increased over that produced when tolbutamide alone was used. The embryos were also placed in a solution containing radioactive Na^{22} to which had been added a teratogenic concentration of tolbutamide. The sodium was present in the same concentration as in a medium which allowed the fish to develop normally; the radioactivity was just a means of following the sodium concentration. By measuring the counts of radioactive sodium over a number of days, it was found that a different turnover pattern for Na^{22} was present when the drug tolbutamide was present in the medium. It had been shown previously that the exposure of the Medeka fish embryo to a high concentration of potassium caused malformations while a higher than normal concentration of sodium accelerated the development of the embryo. Since the glucose and the concentration of sodium used here were in themselves non-teratogenic, Smithberg concludes that this evidence points to the action of the teratogenic tolbutamide being a change in the permeability of the plasma membrane, which in turn upsets the internal environment of the cells. An alternative hypothesis, he admits, is that the drug enters the cell and acts as a poison or metabolic inhibitor.

The predominance of the circulatory defects in the above experiment reminds us of an old theory, put forth by Keith in 1940, namely that the abnormalities are due to temporary or permanent breakdown in the circulatory system. Thus the mechanism of action would include the concept of the drug altering the circulatory system, which in turn would affect the other developing organs. Although some experiments with hypoxia, excess carbon dioxide, and interference with the umbilical artery provide support that this is possible in some cases, this blanket explanation cannot account for all the abnormalities observed.

Many experiments, using animals from monkeys and ungulates to minnows, have been carried out with a host of teratogens. Often the results fit the principles we have outlined; yet often they do not. Sometimes the results of similar experiments are contradictory. All too often the results are totally inexplicable. Who can interpret the following? Carbon gas acting on hen's eggs has produced deformities in the posterior parts of the nervous system so that there appears to be a differential sensitivity of the somites of the nervous system. A host of experiments with trypan blue on rats, and guinea pigs have produced many cardiac lesions. One study of three commercial preparations of trypan blue showed that two preparations produced marked teratogenesis and one was inactive, yet one of the teratogens had a lower L.D. 50 than the non-teratogen. (The amount of azo dye used in terms of titratable azo linkage was the same in all three cases).

Perhaps, as some critics have suggested, some of the research is "unrealistic" in that the doses are hundreds of times that which is ever used in humans, and that perhaps we are compounding the problem by doing this. Dihydrostreptomycin is teratogenic to the chick embryo only in concentrations which are never reached on a percentage-body-weight scale in even the most vigorous human treatment. However it is too early to evaluate the worth of such experiments; they may still help us solve problems.

Prevention of Human Malformations

In the section on human material some suggestions were made about what might well be avoided in early pregnancy. It is true that extensive experiments with new drugs on pregnant animals of many species and strains, using varying doses over varying periods, might disclose a new teratogen. However, we have seen that these experiments never exclude the possibility of some new drug producing abnormalities solely in the human race. The ultimate experiment is still the use of the drug on human beings, and having evaluated the risk involved and the need for a new drug there seems to be little alternative but to proceeding with our trial. Perhaps better reporting or even compulsory reporting of congenital malformations and better lines of communication to those who develop and distribute the drug would be of help.

Much research has been done; much has been learned; further research has been stimulated. Socrates was said to be the wisest man in all Greece because he alone knew "that he knew not", and Saint Paul is quoted as saying: "Now, I know, . . . in part." Let us end then on that same note. The central problem, the mechanism by which thalidomide and other agents can produce congenital abnormalities, remains unsolved. Yet, now, we know . . . in part.

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Abstracts

Ann. of Int. Med., Oct. 1963, p. 495. *Primary Hyperlipidemias and Their Management,* P. T. Kuo, D. R. Bassett

Primary hyperlipidemias are clinical states in which there are genetic abnormalities in the plasma and tissue lipids. They differ in both type and production of the abnormalities. The various types of hyperlipidemias are distinguished by the authors by the character of the serum lipids, fatty acid composition of the adipose tissue and by the post-heparin plasma lipolytic activity.

Using clinical and laboratory data, the various clinical entities were classified as follows: hypercholesterolemia of a pure type and a type in which there is also varying degrees of hyperglyceridemia. Hyperglyceridemias were so heterogeneous as to be difficult to classify but it is possible that there are fat-induced, carbohydrate-induced and mixed hyperglyceridemias.

The authors discuss treatment of the various types in detail. In general, the treatment must be individualized according to the patient not to the disease but reduction in caloric intake is the mainstay of treatment.

Arch of Diseases in Childhood, Vol. 38, 1963, p. 193 *Diffuse Cerebral Degeneration in Infancy (Alpers' Disease)* W. Blackwood et al.

This diffuse degeneration of cerebral gray matter may be associated with epilepsy, spasticity, myclonus and dementia. The authors present the case histories of five cases including the pathological findings of the four who died.

Various possible etiological factors are discussed; these include heredity, birth or post partum anoxia and metabolic factors.

Ann. of Int. Med., Oct. 1963, p. 521
Wegener's Granlomatosis, D. Bergman et al.

Wegener's granulomatosis is a rare disease consisting of necrotizing granulomatous lesions of the respiratory system, disseminated arteritis and terminal glomerulonephritis. The clinical features of the disease resemble closely those of periarteritis nodosa, rheumatoid arthritis and Henoch-Schönlein Disease.

In this article, four cases of Wegener's granulomatosis are presented. All cases ended fatally. One case was typical of the disease; the rest showed variations. Treatment was unsuccessful although the use of steroids in the disseminated stage seemed helpful. Three of the four patients died in fulminating renal failure and the fourth of respiratory complications.

Arch. of Ophthalmology, Jan. 1964, p. 4
Behçet's Disease, J. G. Mamo, A. Baghdassarian

Behçet's disease is an ancient disease found in the eastern Mediterranean and Middle Eastern countries. It is a chronic disease with recurrent remissions and exacerbations. It consists primarily of aphthous mouth and genital lesions and hypopyon iritis. It usually results in blindness.

The etiology is unknown although infection, allergy and vascular disorders have all been considered as possibilities. There is no known treatment. With no central nervous system involvement the prognosis for life is good but for vision the prognosis is always poor.

Br. J. of Psychiatry, Jan. 1964, p. 101.

The Growth Pattern of Psychotic Boys, G. Dutton

Previous studies having suggested that there was a physical superiority of a normal over a psychotic uniovular twin, the author studied the growth pattern of twenty-five boys who had been considered psychotic from an early age. The parameters studied were full height, total body weight, skeletal and sexual maturity.

Height: the mean of the group was within normal limits but 26% of the group were significantly retarded.

Weight: this was difficult to evaluate since the patients may have been over- or undereating because of their psychiatric difficulties but the results suggest that many were heavier than normal for their height.

Skeletal Age: 17% of the group were retarded.

Sexual Maturity: all but one member of the group studied was normal.

The results suggest that in a proportion of cases there is a lag or failure in linear growth and skeletal maturation although sexual development was normal.

Br. J. of Urology, September 1963, p. 293.

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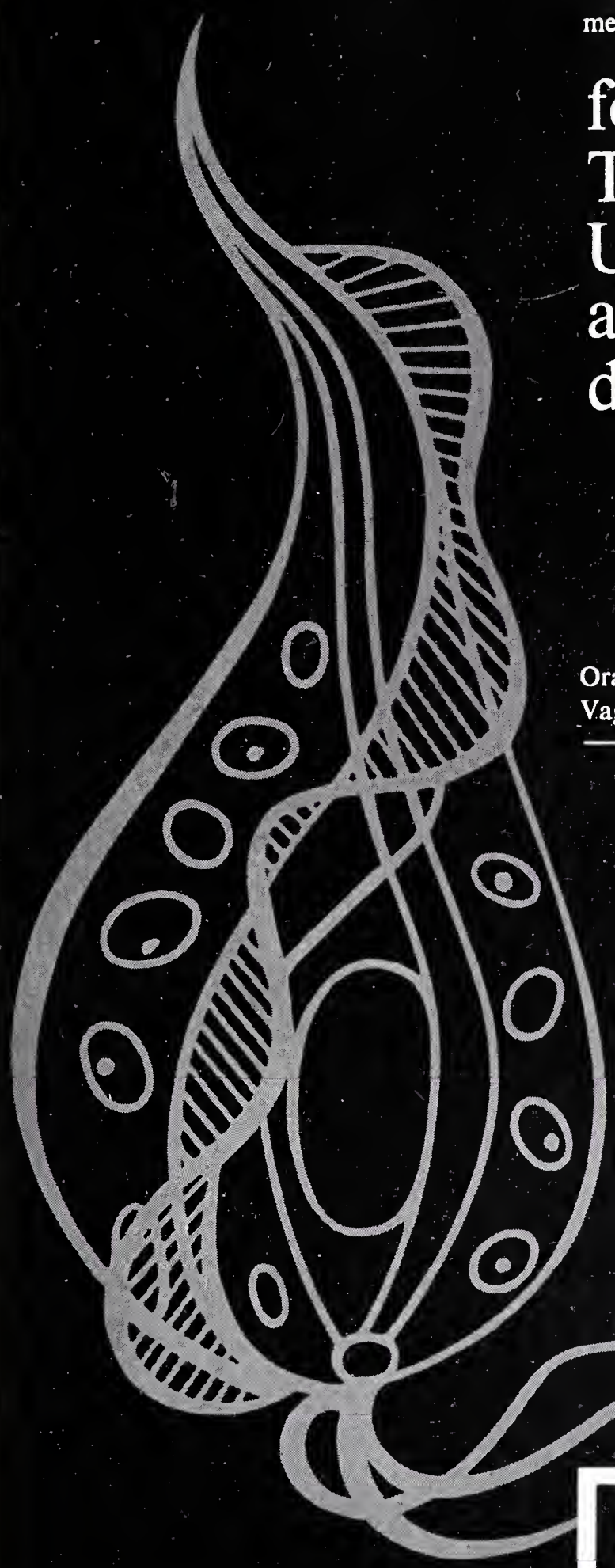

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